10 Environmental Tobacco Smoke

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Extensive toxicological, experimental, and epidemiological data, largely collected since the 1950s, have established that active cigarette smoking is the major preventable cause of morbidity and mortality in the United States; see reports of the U.S. Department of Health Education and Welfare (DHEW), U.S. Environmental Protection Agency (EPA), National Center for Health Statistics (1979), and U.S. Department of Health and Human Services (DHHS, 1989). More recently, since the 1970s, involuntary exposure to tobacco smoke has been investigated as a risk factor for disease; it has also been found to be a cause of preventable morbidity and mortality in nonsmokers. The 1986 report of the Surgeon General on smoking and health and a report by the National Research Council, also published in 1986, comprehensively reviewed the data on involuntary exposure to tobacco smoke and reached comparable conclusions with significant public health implications (see (DHHS, 1986b; NRC, 1986a). Both reports concluded that involuntary smoking causes disease in nonsmokers. Subsequently the Environmental Protection Agency reached a similar conclusion in its 1992 risk assessment, which classified environmental tobacco smoke as a class A carcinogen (EPA, 1992). These conclusions have already had significant impact on public policy and public health.

This chapter summarizes the converging and now extensive evidence on the health effects of involuntary exposure to tobacco smoke. Although the initial research on involuntary smoking addressed respiratory effects, more recent investigations have examined associations with diverse health effects including nonrespiratory cancers, ischemic heart disease, age at menopause, sudden infant death syndrome, and birth weight. This chapter covers the findings on the respiratory effects of passive smoking and also the newer evidence on other effects published since the 1986 reports of the Surgeon General and the National Research Council. The evidence on involuntary exposure to tobacco smoke is now voluminous, and consequently this review is selective in its citations. The most recent compilation of the evidence can be found in the 1997 report of the California Environmental Protection Agency, "Health Effects of Exposure to Environmental Tobacco Smoke" (Cal EPA, 1997).

This review, which updates a 1991 publication, comprehensively covers the newer evidence, including cardiovascular disease, asthma and ear disease in children, and sudden infant death syndrome (SIDS). It does not attempt full coverage of the evidence on health effects of passive smoking for which causal conclusions had already been reached in 1991: lung cancer and respiratory symptoms and lung function in children. The California report provides in-depth reviews and citations to the literature. Respiratory effects of passive

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smoking have also been covered in a recent series of systematic reviews published in *Thorax* (Strachan and Cook, 1997, 1998a, b; Anderson and Cook, 1997, Cook and Strachan, 1997) and in the *British Medical Journal* (Hackshaw, Law, and Wald, 1997; Law and Hackshaw, 1997). These reviews provide the basis for conclusions on passive smoking in the 1998 Report of the Scientific Committee on Tobacco and Health from the United Kingdom (Scientific Committee on Tobacco and Health and HSMO, 1998).

EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE (ETS)

Characteristics of Environmental Tobacco Smoke

Nonsmokers inhale ETS, the combination of the sidestream smoke that is released from the cigarette's burning end and the mainstream smoke exhaled by the active smoker (First, 1985). The inhalation of ETS is generally referred to as passive smoking or involuntary smoking. The exposures of involuntary and active smoking differ quantitatively and, to some extent, qualitatively (NRC, 1981, 1986 a, b; DHHS, 1984, 1986a, b; EPA, 1992; Guerin, Jenkins, and Tomkins, 1992). Because of the lower temperature in the burning cone of the smoldering cigarette, most partial pyrolysis products are enriched in sidestream as compared to mainstream smoke. Consequently sidestream smoke has higher concentrations of some toxic and carcinogenic substances than mainstream smoke; however, dilution by room air markedly reduces the concentrations inhaled by the involuntary smoker in comparison to those inhaled by the active smoker. Nevertheless, involuntary smoking is accompanied by exposure to toxic agents generated by tobacco combustion (NRC, 1981, 1986a, b; DHHS, 1984,1986a, b; EPA, 1992).

Environmental Tobacco Smoke Concentrations

Tobacco smoke is a complex mixture of gases and particles that contains myriad chemical species (DHEW, 1979; DHHS, 1984; Guerin, Jenkins, and Tomkins, 1992). Not surprisingly, tobacco smoking in indoor environments increases levels of respirable particles, nicotine, polycyclic aromatic hydrocarbons, carbon monoxide (CO), acrolein, nitrogen dioxide (NO_2), and many other substances. Tables 10-1 and 10-2 provide summaries of data from some recent studies (Hammond, 1999), and Table 10-3 considers some earlier studies. The extent of the increase in concentrations of these markers varies with the number of smokers, the intensity of smoking, the rate of exchange between the indoor air and with the outdoor air, and the use of air-cleaning devices. Ott (1999) has used mass balance models to characterize factors influencing concentrations of tobacco smoke indoors. Using information on the source strength (i.e., the generation of emissions by cigarettes) and on the air exchange rate, researchers can apply mass balance models to predict tobacco smoke concentrations. Such models can be used to estimate exposures and to project the consequences of control measures.

Several components of cigarette smoke have been measured in indoor environments as markers of the contribution of tobacco combustion to indoor air pollution. Particles have been measured most often because both sidestream and mainstream smoke contain high concentrations of particles in the respirable size range (NRC, 1986; DHHS, 1986). Particles are a nonspecific marker of tobacco smoke contamination, however, because numerous sources other than tobacco combustion add particles to indoor air. Other, more specific markers have also been measured, including nicotine, solanesol, and ultraviolet light (UV) absorption of particulate matter (Guerin, Jenkins, and Tomkins, 1992). Nicotine can be measured with active sampling methods and also using passive diffusion badges (Leaderer and Hammond, 1991; Guerin, Jenkins, and Tomkins, 1992). Studies of levels of

TABLE 10-1 Occupational ETS Exposures in Non-office Settings (Nonsmokers Only)

Company Type	Year Sampled	Number of Samples	Mean	Standard Deviation	Geometric Mean	Concentration of Nicotine, μg/m³ Minimum	Median	Maximum
Smoking allowed								
Specialty chemicals	1991–92	8	0.60	0.91	0.24	<0.05	0.46	2.78
Railroad workers (personal)	1983–84	152	0.80	3.30	0.18	<0.1	0.10	38.10
Tool manufacturing	1991–92	13	1.59	1.05	1.16	0.15	1.85	3.40
Textile finishing b	1991–92	11	1.74	1.69	1.10	0.31	0.93	5.09
Labels and paper products	1991–92	1	2.31				2.31	
Die manufacturer	1991–92	12	2.70	1.27	2.46	1.23	2.41	5.42
Sintering metal	1991–92	12	2.88	2.59	2.11	0.62	2.24	9.72
Newspaper B	1991–92	5	2.96	1.37	2.68	1.23	2.78	4.63
Miscellaneous	< 1990	282	4.30	11.80	1.70	< 1.6	< 1.6	126.00
Textile finishing, A	1991–92	11	4.33	8.82	1.77	0.46	1.39	30.71
Flight attendants (personal)	1988	16	4.70	4.00	2.32	0.10	4.20	10.50
Fire fighters A [a]	1991–92	16	5.39	3.81	4.08	1.20	4.84	13.42
Fire fighters B	1991–92	24	5.83	6.77	3.83	0.71	3.65	27.50
Barber shop (personal)	1986–87	2	8.80			4.00		13.70
Hospital (personal)	1986–87	5	24.80	22.80	16.80	6.30	10.00	53.20
Smoking restricted								
Work clothing	1991–92	9	0.17	0.32	0.06	< 0.05	< 0.05	0.93
Filtration products	1991–92	10	0.32	0.87	0.08	< 0.05	< 0.05	2.78
Film and imaging	1991–92	6	0.82	0.83	0.39	< 0.05	0.70	2.16
Fiber optics	1991–92	13	1.34	2.79	0.63	0.20	0.64	10.57
Newspaper A	1991–92	4	4.86	6.65	2.62	0.93	1.85	14.81
Valve manufacturer	1991–92	10	5.80	7.85	3.62	1.16	3.26	27.31
Rubber products	1991–92	2	5.85	5.36	4.18	2.06	5.85	9.64

TABLE 10-1 (*Continued*)

Company Type	Year Sampled	Number of Samples	Mean	Standard Deviation	Geometric Mean	Concentration of Nicotine, μg/m³		
						Minimum	Median	Maximum
				Smoking Prohibited				
Infrared and imaging systems	1991–92	1	< 0.05				< 0.05	
Hospital products	1991–92	5	0.08	0.17	< 0.05	< 0.05	< 0.05	0.39
Weapons systems	1991–92	12	0.08	0.20	< 0.05	< 0.05	< 0.05	0.63
Aircraft components	1991–92	12	0.20	0.18	0.13	< 0.05	0.21	0.61
Radar communications components	1991–92	13	0.31	0.36	0.14	< 0.05	0.26	1.08
Computer chip equipment	1991–92	10	0.51	0.33	0.41	0.15	0.39	1.08

Source: Hammond (1999).

[a] Omits one data point, 101 μg/m³.

TABLE 10-2 Nicotine Concentrations in Homes

	Year Sampled	Number of Samples	Concentration of Nicotine, $\mu g/m^3$: Mean	Standard Deviation	Minimum	Median	Maximum
North Carolina homes (weekly)	1988	13	1.50	1.10	1.00	1.40	4.40
Personal (each sampled 3 ×)	1988	15					
Males (personal: 16 hours)[a]	1993–94	86	2.13			1.29	> 8.08
New York homes (weekly)	1986	47	2.20		0.10	1.00	9.40
Females (personal: 16 hours)[a]	1993–94	220	2.93			1.14	> 7.81
North Carolina homes (14 hours: 5 p.m. to 7 a.m.)	1986	13	3.74			3.3[c]	6.5
Minnesota homes (weekly)	1989[c]	25	5.80		0.10	3.00	28.60

[a] 16 hour average; "away from work."
[b] Ninety-fifth percentile, as noted in the chapter.
[c] Assumed 16 hour exposure.

Source: Hammond (1999).

TABLE 10-3 Selected Studies of Tobacco Smoke Component Concentrations in Various Environments in the 1970s and 1980s

Reference	Location	Component	Mean Concentration
Badre et al. (1978)	Room, 18 smokers	Acrolein	0.19 $\mu g/m^3$
Badre et al. (1978)	Room, 18 smokers	Benzene	0.11 $\mu g/m^3$
Wallace (1987)	NJ homes, smokers	Benzene	16 $\mu g/m^3$, overnight
	NJ homes, nonsmokers	Benzene	8.4 $\mu g/m^3$, overnight
Chappell and Parker (1977)	Offices	Carbon monoxide	2.5 ppm, samples 2–3 min
Chappell and Parker (1977)	Nightclubs	Carbon monoxide	13.0 ppm, sampled 2–3 min
Hinds and First (1975)	Restaurant	Nicotine	5.2 $\mu g/m^3$, sampled 2.5 h
Hinds and First (1975)	Train	Nicotine	6.3 $\mu g/m^3$, sampled 2.5 h
Muramatsu et al. (1984)	Cafeterias	Nicotine	26.4 $\mu g/m^3$
Weber and Fischer (1980)	Offices	Nitrogen dioxide	24 ppb
Repace and Lowrey (1980)	Cocktail party	Particles	351 $\mu g/m^3$, 15 min sample
	Bowling alley	Particles	202 $\mu g/m^3$, 20 min sample
	Bar	Particles	334 $\mu g/m^3$, 26 min sample
Spengler et al. (1981)	Residences, $\geq$ 2 smokers	Particles	70 $\mu g/m^3$, 24 h samples
	Residences, 1 smoker	Particles	37 $\mu g/m^3$, 24 h samples
Henderson et al. (1989)	Residences, cigarette smoking	Nicotine	3.4 $\mu g/m^3$, 14 h samples
	Residences, no cigarette smoking	Nicotine	0.3 $\mu g/3^3$, 14 h samples

Source: Guerin, Jenkins, and Tomkins (1992).

ETS components have been conducted largely in public buildings; fewer studies have been conducted in homes and offices (NRC, 1986a; DHHS, 1986b).

The contribution of various environments to personal exposure to tobacco smoke varies with the time-activity pattern, namely the distribution of time spent in different locations. Time-activity patterns may heavily influence lung airway exposures in particular environments for certain groups of individuals. For example, exposure in the home predominates for infants who do not attend day care (Harlos et al., 1987). For adults residing with nonsmokers, the workplace may be the principal location where exposure takes place. A recent nationwide study assessed exposures of nonsmokers in 16 metropolitan areas of the United States (Jenkins et al., 1996). This study, involving 100 persons in each location, was directed at workplace exposure and included measurements of respirable particulate matter and other markers. The results showed that in 1993 and 1994, exposures to ETS in the home were generally much greater than those in the workplace.

The contribution of smoking in the home to indoor air pollution has been demonstrated by studies using personal monitoring and monitoring of homes for respirable particles. In one of the early studies, Spengler et al. (1981) monitored homes in six U.S. cities for respirable particle concentrations over several years and found that a smoker of one pack of cigarettes daily contributed about 20 $\mu g/m^3$ to 24 hour indoor particle concentrations. In homes with two or more heavy smokers, this study showed that the pre-1987 24 hour National Ambient Air Quality Standard (NAAQS) of 260 $\mu g/m^3$ for total suspended particulates could be exceeded. Because cigarettes are not smoked uniformly over the day, higher peak concentrations must occur when cigarettes are actually smoked. Spengler et al. (1985) measured the personal exposures to respirable particles sustained by nonsmoking adults in two rural Tennessee communities. The mean 24 hour exposures were substantially higher for those exposed to smoke at home: 64 $\mu g/m^3$ for those exposed versus 36 $\mu g/m^3$ for those not exposed.

In several studies, small numbers of homes have been monitored for nicotine, which is a vapor-phase constituent of ETS. In a study of ETS exposure of day-care children, average nicotine concentration during the time that the ETS-exposed children were at home was 3.7 $\mu g/m^3$; in homes without smoking, the average was 0.3 $\mu g/m^3$ (Henderson, et al., 1989). Coultas and colleagues (Coultas et al., 1990a measured 24 hour nicotine and respirable particle concentrations in 10 homes on alternate days for a week and then on five more days during alternate weeks. The mean levels of nicotine were comparable to those in the study of Henderson et al. (1989), but some 24 hour values were as high as 20 $\mu g/m^3$. Nicotine and respirable particle concentrations varied widely in the homes.

The total exposure assessment methodology (TEAM) study, conducted by the U.S. Environmental Protection Agency, provided extensive data on concentrations of 20 volatile organic compounds in a sample of homes in several communities (Wallace and Pellizzari, 1987). Indoor monitoring showed increased concentrations of benzene, xylenes, ethylbenzene, and styrene in homes with smokers compared to homes without smokers.

More extensive information is available on levels of ETS components in public buildings and workplaces of various types (Hammond, 1999; Guerin, Jenkins, and Tomkins, 1992) (Tables 10-1 and 10-3). Monitoring in locations where smoking may be intense, such as bars and restaurants, has generally shown elevations of particles and other markers of smoke pollution where smoking is taking place (DHHS, 1986b; NRC, 1986a). For example, Repace and Lowrey (1980) in an early study used a portable piezobalance to sample aerosols in restaurants, bars, and other locations. In the places sampled, respirable particulate levels ranged up to 700 $\mu g/m^3$, and the levels varied with the intensity of smoking. Similar data have been reported for the office environment (DHHS, 1986b; NRC, 1986a; Guerin, Jenkins, and Tomkins, 1992; Cal EPA, 1997). Recent studies indicate low concentrations in many workplace settings, reflecting declining smoking prevalence in recent years and changing practices of smoking in the workplace. Using passive nicotine samplers, Hammond (1999) showed that worksite smoking policies can sharply reduce ETS exposure.

Transportation environments may also be polluted by cigarette smoking. Contamination of air in trains, buses, automobiles, airplanes, and submarines has been documented (DHHS, 1986b; NRC, 1986a). A National Research Council Report (NRC, 1986b) on air quality in airliners summarized studies for tobacco smoke pollutants in commercial aircraft. In one study, during a single flight, the NO_2 concentration varied with the number of passengers with a lighted cigarette. In another study, respirable particles in the smoking section were measured at concentrations five or more times higher than in the nonsmoking section. Peaks as high as 1000 $\mu g/m^3$ were measured in the smoking section. Mattson and colleagues (1989) used personal exposure monitors to assess nicotine exposures of passengers and flight attendants. All persons were exposed to nicotine, even if seated in the nonsmoking portion of the cabin. Exposures were much greater in the smoking than in the nonsmoking section and were also greater in aircraft with recirculated air.

Biological Markers of Exposure

Biological markers can be used to describe the prevalence of exposure to environmental tobacco smoke, to investigate the dosimetry of involuntary smoking, and to validate questionnaire-based measures of exposure. In both active and involuntary smokers, the detection of tobacco smoke components or their metabolites in body fluids or alveolar air provides evidence of exposure to tobacco smoke, and levels of these markers can be used to gauge the intensity of exposure. The risk of involuntary smoking has also been estimated by comparing levels of biological markers in active and involuntary smokers.

At present, the most sensitive and specific markers for tobacco smoke exposure are nicotine and its metabolite, cotinine (NRC, 1986a; Jarvis and Russell, 1984; DHHS, 1988). Neither nicotine nor cotinine is usually present in body fluids in the absence of exposure to tobacco smoke, although unusually large intakes of some foods could produce measurable levels of nicotine and cotinine (Idle, 1990). Cotinine, formed by oxidation of nicotine by cytochrome P-450, is one of several primary metabolites of nicotine (DHHS, 1988). Cotinine itself is extensively metabolized, and only about 17% of cotinine is excreted unchanged in the urine.

Because the circulating half-life of nicotine is generally shorter than 2 hours (Rosenberg et al., 1980), nicotine concentrations in body fluids reflect more recent exposures. In contrast, cotinine has a half-life in the blood or plasma of active smokers of about 10 hours (DHHS, 1988; Kyerematen et al., 1982; Benowitz et al., 1983); hence cotinine levels provide information about more chronic exposure to tobacco smoke in both active and involuntary smokers. Whether cotinine has the same half-life in plasma, saliva, and urine has been uncertain, as is the choice of the optimal body fluid for measuring cotinine for research purposes (Jarvis et al., 1988; Wall et al., 1988; Haley et al., 1989). Concerns about nonspecificity of cotinine, arising from eating nicotine-containing foods, have been set aside (Benowitz, 1996). Thiocyanate concentration in body fluids, concentration of CO in expired air, and carboxyhemoglobin level distinguish active smokers from nonsmokers but are not as sensitive and specific as cotinine for assessing involuntary exposure to tobacco smoke (Hoffman et al., 1984; Jarvis and Russell, 1984).

Cotinine levels have been measured in adult nonsmokers and in children (Table 10-4) (Benowitz, 1996). In the studies of adult nonsmokers, exposures at home, in the workplace, and in other settings determined cotinine concentrations in urine and saliva. The cotinine levels in involuntary smokers ranged from less than 1% to about 8% of cotinine levels measured in active smokers. Smoking by parents was the predominant

TABLE 10-4 Cotinine Concentrations in Nonsmokers and Smokers (Selected Studies)

Study	Number of Subjects	Smoking Status	Exposure Level	Plasma or Serum Cotinine (ng/ml)	Urine Cotinine (ng/ml)	Salivary Cotinine (ng/ml)
Jarvis et al. (1984)	46	Nonsmokers	No exposure	0.8	1.5	0.7
	54	Nonsmokers	Exposed	2.0	7.7	2.5
Wald and Ritchie (1984)	101	Nonsmokers	Wife nonsmoker		8.5 (SE* ± 1.3, median 5.0)	
	20	Nonsmokers	Wife smoker		25.2 (SE ± 14.8, median 9.0)	
Wald et al. (1984)	43	Nonsmokers	0–1.5 hours ETS* exposure / week		1.8	
	47	Nonsmokers	1.5–4.5 hours ETS exposure / week		3.4	
	43	Nonsmokers	4.5–8.6 hours ETS exposure / week		5.3	
	43	Nonsmokers	8.6–29 hours ETS exposure / week		14.7	
	45	Nonsmokers	20–80 hours ETS exposure / week		29.6	
Jarvis et al. (1985)	269	Nonsmokers, children	Neither parent smoked			
	96	Nonsmokers, children	Father smoked			
	76	Nonsmokers, children	Mother smoked			
	128	Nonsmokers, children	Both parents smoked			
Coultas et al. (1986)	68	Nonsmokers aged <5 years	No smoker in home			
	41	Nonsmokers aged <5 years	1 smoker in home			
	21	Nonsmokers aged <5 years	2 or more smokers in home			
	200	Nonsmokers aged 5–17 years	No smoker in home			
	96	Nonsmokers aged 5–17 years	1 smoker in home			
	25	Nonsmokers aged 5–17 years	2 or more smokers in home			
	316	Nonsmokers aged >17 years	No smoker in home			
	60	Nonsmokers aged >17 years	1 smoker in home			
	12	Nonsmokers aged >17 years	2 or more smokers in home			
Strachan et al. (1989)	405	Nonsmokers, age 7 years	No smokers in home			
	241	Nonsmokers, age 7 years	1 smoker in home			
	124	Nonsmokers, age 7 years	2 or more smokers in home			

TABLE 10-4 *(Continued)*

Study	Number of Subject	Smoking Status	Exposure Level	Plasma or Serum Cotinine (ng/ml)	Urine Cotinine (ng/ml)	Salivary Cotinine (ng/ml)
Thompson et al. (1990)	158	Nonsmokers	Lives alone or with nonsmoker		4.4 (geometric mean) (95% CI: 3.6–5.4)	
	26	Nonsmokers	Lives with smoker		11.4 (geometric mean) (95% CI: 6.9–18.9)	
Cummings et al. (1990)	162	Nonsmokers	No exposure past 4 days		6.2 (mean)	
	208	Nonsmokers	1–2 exposures past 4 days		7.8 (mean)	
	152	Nonsmokers	3–5 exposures past 4 days		9.8 (mean)	
	141	Nonsmokers	6 or more exposures		12.5 (mean)	
Tunstall-Pedoe et al. (1991)	1873	Nonsmokers, male		0.68 (median)		
	1940	Smokers, male		240 (median)		
	2270	Nonsmokers, female		0.10 (median)		
Cook et al. (1994)	1260	Nonsmokers, aged 5–7 years	No smokers in home			0.29 (geometric mean) (95% CI: 0.28–0.31)
	293	Nonsmokers, aged 5–7 years	Mother smoker			2.2 (geometric mean) (95% CI: 1.9–2.5)
	521	Nonsmokers, aged 5–7 years	Father smoker			1.2 (geometric mean) (95% CI: 1.1–1.3)
	553	Nonsmokers, aged 5–7 years	Mother and father smokers			4.0 (geometric mean) (95% CI: 3.7–4.4)
Riboli et al. (1990)	629	Nonsmokers, females from 10 countries	No home or work ETS exposure		2.7 ng / mg creatinine	
	210	Nonsmokers, females from 10 countries	Exposure at work but not at home		4.8 ng / mg creatinine	
	359	Nonsmokers, females from 10 countries	Exposure at home but not at work		9.0 ng / mg creatinine	
	124	Nonsmokers, females from 10 countries	Exposure at home and at work		10.0 ng / mg creatinine	
Pirkle et al. (1996)	1071	Nonsmokers, aged 4–11 years	No home ETS exposure	0.12 (geometric mean) (95% CI: 0.10–0.14)		

713	Nonsmokers, aged 4–11 years	Home ETS exposure only	1.13 (geometric mean) (95% CI: 0.98–1.34)
379	Nonsmokers, aged 12–16 years	No home ETS exposure	0.11 (geometric mean) (95% CI: 0.10–0.15)
268	Nonsmokers, aged 12–16 years	Home ETS exposure only	0.81 (geometric mean) (95% CI: 0.62–1.04)
3154	Nonsmokers, aged ≥17 years	No home or work ETS exposure	0.12 (geometric mean) (95% CI: 0.11–0.14)
1332	Nonsmokers, workers aged ≥17 years	No home or work ETS exposure	0.13 (geometric mean) (95% CI: 0.12–0.15)
779	Nonsmokers, workers aged ≥17 years	Work ETS exposure only	0.32 (geometric mean) (95% CI: 0.28–0.36)
315	Nonsmokers, workers aged ≥17 years	Home ETS exposure only	0.65 (geometric mean) (95% CI: 0.52–0.81)
246	Nonsmokers, workers aged ≥17 years	Home and work ETS exposure	0.93 (geometric mean) (95% CI: 0.76–1.13)

Source: Benowitz (1996).

determinant of the cotinine levels in their children. For example, Greenberg et al. (1984) found significantly higher concentrations of cotinine in the urine and saliva of infants exposed to cigarette smoke in their homes than in unexposed controls. Urinary cotinine levels in the infants increased with the number of cigarettes smoked during the previous 24 hours by the mother. In a study of school children in England, salivary cotinine levels rose with the number of smoking parents in the home (Jarvis et al., 1985). In a study of a national sample of participants in the Third National Health and Nutrition Examination Survey conducted in 1988 to 1991, 88% of nonsmokers had a detectable level of serum cotinine using liquid chromatography–mass spectrometry as the assay method (Pirkle et al., 1996). Cotinine levels in this national sample increased with the number of smokers in the household and the hours exposed in the workplace.

The results of studies on biological markers have important implications for research on involuntary smoking and add to the biological plausibility of associations between involuntary smoking and disease documented in epidemiological studies (Benowitz, 1996). The data on marker levels provide ample evidence that involuntary exposure leads to absorption, circulation, and excretion of tobacco smoke components. The studies of biological markers also confirm the high prevalence of involuntary smoking, as ascertained by questionnaire (Benowitz, 1996; Coultas et al., 1987; Pirkle et al., 1996). The observed correlations between reported exposures and levels of markers suggest that questionnaire methods for assessing recent exposure have some validity.

Comparisons of levels of biological markers in smokers and nonsmokers have been made in order to estimate the relative intensities of active and involuntary smoking. However, proportionality cannot be assumed between the ratio of the levels of markers in passive and active smokers and the relative doses of other tobacco smoke components. Nonetheless, several investigators have previously attempted to characterize involuntary smoking in terms of active smoking. For example, Foliart and colleagues (Foliart, Benowitz, and Becker, 1983) measured urinary excretion of nicotine in flight attendants during an 8 hour flight and estimated that the average exposure was 0.12 to 0.25 mg of nicotine. Russell, West, and Jarvis (1985) compared nicotine levels in nonsmokers exposed to tobacco smoke with levels achieved following infusion of known doses of nicotine. On the basis of this comparison, the investigators estimated that the average rate of nicotine absorption was 0.23 mg per hour in a smoky tavern, 0.36 mg per hour in an unventilated smoke-filled room, and 0.014 mg per hour from average daily exposure. In active smokers the first cigarette of the day resulted in absorption of 1.4 mg of nicotine.

Exposure Assessment

The information on the health effects of involuntary smoking has been largely derived from observational epidemiological studies. In these studies exposure to ETS has been estimated primarily by responses to questionnaires concerning the smoking habits of household members or of fellow employees; attempts have been made to quantitate exposure by determining the number of cigarettes smoked by family members and the duration of exposure. Biomarkers have also been used in some studies. Limitations of the questionnaire approach were discussed extensively in the 1986 report of the Surgeon General (DHHS, 1986b). The general topic is treated in a 1997 review by the Jaakkolas (Jaakkola and Jaakkola, 1997).

A number of studies have addressed questionnaires and biological markers for assessing exposure to ETS. In studies of lung cancer and passive smoking, questionnaires have been used to assess the smoking habits of spouses and, in a few studies, of parents. Two studies evaluated the reliability of questionnaires on lifetime exposure (Pron et al., 1988; Coultas, Peake, and Samet, 1989). Both showed a high degree of repeatability for questions concerning whether a spouse had smoked but lower reliability for responses concerning quantitative aspects of exposure. Because validity could not be assessed directly, reliability was used as a measure of information quality.

Several studies have assessed the validity of subjects' reports on smoking by parents and spouses. Sandler and Shore (1986) compared responses on parents' smoking given by cases and controls with responses given by the parents or siblings of the index subjects. Concordance was high for whether the parents had ever smoked. Responses concerning numbers of cigarettes smoked did not agree as highly. In a follow-up study of a nationwide sample, children's responses on smoking by their deceased parents closely agreed with the information given 10 years previously by the parents (McLaughlin et al., 1987). A number of studies have shown that people correctly report the smoking habits of their spouses (DHHS, 1990a). In a study of nonsmokers in Buffalo, index subjects' reports agreed well with reports from parents or siblings, spouse or children, and coworkers concerning exposure during childhood, at home, and at work, respectively (Cummings et al., 1989).

Nicotine is present primarily as a vapor-phase component in ETS and can thus be sampled using a diffusion-based monitor (Hammond and Leaderer, 1987). Coghlin, Hammond, Gann and colleagues (1989) described the use of a passive nicotine monitor as well as a questionnaire and diary approach for characterizing exposure to ETS. In a sample of 19 volunteers, they found a strong correlation between the monitored nicotine exposure and a questionnaire-based index. The sampling lasted only a week, however, and the diary method would be too cumbersome to implement among all participants in a large epidemiological study. Coultas et al. (1990b) measured personal exposure to ETS using a personal pump and a collection system for nicotine. In a small sample of volunteers, they established the feasibility of this approach.

Although biological markers have provided important evidence of population exposures, the utility of cotinine as an indicator of individual exposure has been questioned. Idle (1990) has reviewed the complex metabolism of nicotine and the many factors affecting the relationship between exposure to atmospheric nicotine and the concentration of cotinine in body fluids. He cautions against using any single determination of cotinine as a measure of exposure.

Several epidemiological studies support this concern about the limited validity of a single measurement of cotinine. Spot cotinine levels are not tightly predicted by questionnaire measures of exposures (Coultas, Peake, and Samet, 1989; Cummings et al., 1990), and cotinine levels are highly variable at any particular level of smoking in a household (Coultas et al., 1990a). Thus questionnaires remain the best method for characterizing usual exposure to ETS. However, biological markers and personal monitoring offer complementary approaches for developing more accurate exposure estimates for estimating dose and judging the extent of misclassification introduced by questionnaires.

HEALTH EFFECTS OF INVOLUNTARY SMOKING IN CHILDREN

Fetal Effects

Researchers have demonstrated that active smoking by mothers results in a variety of adverse health effects in children. Some of the health effects result predominantly from transplacental exposure of the fetus to tobacco smoke components. Recently studies have also investigated and demonstrated associations between adverse health effects in children and exposure to ETS. For example, paternal smoking in the presence of a pregnant mother may lead to perinatal health effects manifested upon birth of the baby, and either maternal or paternal smoking in the presence of a newborn child may lead to postnatal health effects in the developing child.

Potential health effects on the fetus resulting from ETS include fetal growth effects (decreased birth weight, growth retardation, or prematurity), fetal loss (spontaneous abortion and perinatal mortality), and congenital malformations. Health effects on the child postnatally, resulting from either ETS exposure to the fetus or to the newborn child, include sudden infant death syndrome (SIDS) and adverse effects on neuropsychological development and physical growth. Possible longer-term health effects of fetal ETS exposure include childhood cancers of the brain, leukemia, and lymphomas, among others.

Biological Plausibility

Fetal exposure to carbon monoxide and nicotine due to ETS may increase risk for perinatal health effects. Carbon monoxide in ETS may contribute to increased concentrations of carbon monoxide and carboxyhemoglobin in the fetus, and the fetus may not be able to physiologically compensate for the reduced oxygen delivery (DHHS, 1980), leading to fetal hypoxia. Chronic fetal hypoxia may lead to impaired development of the fetal central nervous system, with abnormal control of cardiorespiratory activity, and thus to SIDS (Harper and Frysinger, 1988). One study showed increased rates of central apnea in infants of smokers (Toubas et al., 1986).

Exposure to nicotine found in ETS can also alter an infant's catecholamine metabolism and response to hypoxia (Milerad and Sundell, 1993). Furthermore nicotine crossing the placenta may lead to decreased in utero placental perfusion, affecting the fetal cardiovascular system, gastrointestinal system, and central nervous system (Stillman, Rosenberg, and Sachs, 1986). Other constituents of cigarette smoke have also been demonstrated to adversely affect fetal growth (Cal EPA, 1996).

Association between ETS and childhood cancers is biologically plausible due to the presence of carcinogenic tobacco smoke components or metabolites, such as benzene, nitrosamines, urethane, and radioactive compounds, at organ sites of the cancers. In animal studies, neurogenic tumors as well as other tumors were induced after transplacental exposure to a number of compounds present in tobacco smoke, including several nitrosamines. Moreover Huel and colleagues (1989) measured aryl hydrocarbon hydroxylase activity in human placentas of passive smokers; levels were increased in placentas of women passively exposed to tobacco smoke.

Nonfatal Perinatal Health Effects

Fetal Growth Most studies have used paternal smoking as the exposure measure to assess the association between ETS exposure and nonfatal perinatal health effects, such as reduced fetal growth. Low birth weight was first reported in 1957 to be associated with maternal smoking (DHHS, 1980). Extensive studies have since been conducted to assess ETS exposure and birth weight, accounting for gestational age at delivery, multiple births, maternal age, race, parity, maternal smoking, socioeconomic status, and pregnancy history (DHHS, 1994). Exposures have been measured with questionnaires that assess home and work exposure, and in some studies, with the use of biomarkers.

Recent studies continue to report lower birth weight for infants of nonsmoking women passively exposed to tobacco smoke during pregnancy (Martin and Bracken, 1986; Rubin et al., 1986). Haddow and colleagues (1988) used cotinine as a biomarker to measure exposure to ETS; they also adequately controlled for potential confounders. ETS exposure was defined as cotinine levels of 1.1 to 9.9 ng/mL in the fetus born to a nonsmoking mother. Their study demonstrated a decrease of 100 grams in birthweight for fetuses exposed to ETS. The most recent biomarker studies (Eskenazi and Bergmann, 1995; Eskenazi and Trupin, 1995; Martinez et al., 1994) support the findings of Haddow et al. (1988). Other epidemiologic studies assessed ETS exposure from multiple sources through questionnaire (Mainous and Hueston, 1994; Roquer et al., 1995; Rebagliato, Florey, and Bolumar, 1995). While not using a method as specific or sensitive as cotinine measurements, these studies still demonstrated decreases in mean birthweights after adjustment for confounders (20 to 40 g).

Other Effects Other nonfatal perinatal health effects possibly associated with ETS are growth retardation and congenital malformations. Martin and Bracken (1986) demonstrated a strong association with growth retardation in their 1986 study. More recent studies (Roquer et al., 1995; Mainous and Hueston, 1994) have supported this finding; however, these studies had small sample sizes and did not control for potential confounders.

The few studies (Zhang et al., 1992; Savitz, Schwingl, and Keels, 1991; Seidman, Ever-Hadani, and Gale, 1990) conducted to assess the association between paternal smoking and congenital malformations have demonstrated odds ratios ranging from 1.2 to 2.6. The most consistent associations have been found with the central nervous system or neural tube defects. However, due to possible effects of active smoke on the sperm, a causal association between ETS and congenital malformations cannot be concluded.

Fatal Perinatal Health Effects

ETS exposure to the fetus during its development may lead to fatal perinatal health effects such as spontaneous abortion and perinatal mortality. Very few studies have examined the association between ETS exposure and perinatal death. Eight studies have examined neonatal mortality in relation to paternal smoking; a few supported an increase in risk (Comstock and Lundin, 1967; Mau and Netter, 1974; Lindbohm, et al., 1991;Ahlborg, Jr. and Bodin, 1991).

Postnatal Health Effects

ETS exposure due to maternal or paternal smoking may lead to postnatal health effects related to SIDS, physical development, decrements in cognition and behavior, and cancers.

SIDS To date, 10 studies have been directed at the association between SIDS and postnatal maternal ETS exposure; 6 studies have addressed the association between paternal smoking and SIDS, and 4 studies have assessed household smoke exposure and SIDS (Table 10-5). While maternal smoking during pregnancy has been associated with SIDS, these studies measured maternal smoking after pregnancy, along with paternal smoking and household smoking generally. Effects of ETS exposure after birth and maternal smoking during pregnancy cannot be readily separated in many of these studies.

Mitchell and colleagues (Mitchell et al., 1993) demonstrated a significant association (odds ratio, OR = 1.7) between postnatal maternal smoking and SIDS; this association remained significant after adjustment for potential confounders. In their updated study Mitchell and colleagues (Mitchell, Scragg, and Clements, 1995) concluded that while SIDS was associated with postnatal maternal smoking, the elimination of postnatal maternal smoking did not reduce the risk of SIDS, and that prenatal exposure was still the more important risk factor. Similarly Schoendorf and Kiely (1992) demonstrated an adjusted odds ratio of 1.8 for SIDS associated with postnatal ETS exposure. In a larger study Klonoff-Cohen and colleagues (1995) found an adjusted odds ratio of 2.3 for postnatal ETS exposure. Three more studies assessing maternal smoking after pregnancy (Bergman and Wiesner, 1976; McGlashan, 1989; Mitchell et al., 1991) could not assess a possible independent relationship between postnatal smoking and SIDS due to extensive overlap between maternal smoking during and after pregnancy.

TABLE 10-5 Studies Investigating the Association between ETS and SIDS

Study Reference	Location	Outcome Assessed	Exposure	Exposure Ascertainment	Participants	OR	OR Adjusted for:
Bergman and Wiesner (1976)	United States (King County, Washington)	SIDS	Maternal smoking after pregnancy	Mailed questionnaire	56 cases 86 controls	2.4 (1.2, 4.8)	Matched on: date of birth, sex, and race
			Paternal smoking			1.5 (0.7, 3.2)	Not adjusted for maternal smoking
McGlashan (1989)	Tasmania	SIDS	Maternal smoking during and after pregnancy	Interviewed parents	167 cases 334 controls	1.9 (1.2, 2.9)	Matched on sex
			Paternal smoking			"Significantly increased"	
Mitchell et al. (1991)	New Zealand	SIDS	Maternal smoking after pregnancy	Interview with parents or from medical records	128 cases 503 controls	1.8 (1.0, 3.3)	Demographic factors, social factors, breast-feeding, season, sleeping position
Nicholl and O' Cathain (1992)	United Kingdom	SIDS	Paternal smoking		242 cases 251 controls	1.4 (0.8, 2.4)	Spousal smoking matched for date and place of birth
Schoendorf and Kiely (1992)	United States (U.S. National Maternal and Infant Health Survey)	SIDS	Maternal smoking after pregnancy	Interview	435 cases 6000 controls	Whites: 1.8 (1.0, 3.0) Blacks: 2.3 (1.5, 3.7)	Maternal age, education, marital status
Mitchell et al. (1993)	New Zealand	SIDS	Maternal smoking after pregnancy	Interview with parents of from medical records	485 cases 1800 controls	1.7 (1.2, 2.3)	Region, season, breast-feeding, bed sharing, mother's marital status, SES, age, smoking during pregnancy, infant's age, sex, birth
			Paternal smoking			1.4 (1.0, 1.8)	

						weight, race, sleeping, position, smoking by mother, smoking by father, smoking by other household members
Klonoff-Cohen et al. (1995)	United States (southern California)	SIDS	Maternal smoking after pregnancy	200 cases 200 controls	2.3 (1.0, 5.0)	Birth weight, routine sleep position, medical conditions at birth, prenatal care, breast-feeding, maternal smoking during pregnancy
			Same-room, maternal smoking after pregnancy		4.6 (1.8, 11.8)	
			Paternal smoking		3.5 (1.9, 6.8)	
			Same-room, paternal smoking		5.0 (2.4, 11.0)	
Blair et al. (1996)	United Kingdom	SIDS	Paternal smoking	195 cases 780 controls	2.5 (1.5, 4.2)	Maternal, age, marital status, SES, maternal smoking, drug and alcohol use, gestational age, sleeping position, breast-feeding, matched by age and region

Of the six studies conducted to assess the association between paternal smoking and SIDS, four (Nicholl and O'Cathain, 1992; Mitchell et al., 1993; Klonoff-Cohen et al., 1995; Blair et al., 1996) demonstrated elevated risks for SIDS while accounting for maternal smoking either by study design or through analyses, with odds ratios of 1.6, 1.4, 3.5, and 2.5, respectively. Two studies (Bergman and Wiesner, 1976; McGlashan, 1989) demonstrated elevated risks but did not adjust for maternal smoking.

Four studies assessed general household smoke exposure and SIDS. Dose–response relationships were observed by Blair and colleagues (1996), Mitchell and colleagues (1993), and Klonoff-Cohen and colleagues (1995). Klonoff-Cohen and colleagues reported adjusted odds ratios for 1 to 10, 11 to 20, and ≥ 21 cigarettes/day of 2.4, 3.6, and 22.7, respectively. Schoendorf and Kiely (1992) only demonstrated increased risk of SIDS in white infants.

Cognition and Behavior While it is biologically plausible that ETS affects a child's neuropsychological development—perhaps through nicotine's effect on the central nervous system and through the effect of chronic exposure to carbon monoxide—few studies have provided the data needed to examine this relationship independent of prenatal exposure and maternal active smoking. Furthermore cognition and behavior are also measured through a variety of tests, making direct comparisons between studies difficult.

Makin, Fried, and Watkinson (1991) compared cognitive test scores of children of nonsmoking mothers exposed to ETS during pregnancy to children of unexposed mothers. Decrements in test scores were demonstrated for children whose mothers were exposed to ETS during their pregnancy. The much larger study conducted by Eskenazi and Trupin (1995), which used serum cotinine to ascertain ETS exposure, however, failed to detect such an association. Five more studies (Baghurst et al., 1992; Bauman, Koch, and Fisher, 1989; Bauman and Flewelling, 1991; Denson, Nanson, and McWatters, 1975; Weitzman, Gortmaker, and Sobul, 1992) assessing postnatal ETS exposure and cognitive endpoints in children also failed to produce consistent results. While four of the five studies demonstrated modest decrements in performance, the decrements demonstrated by Baghurst and colleagues (1992) were no longer found after adjustment for confounders; Bauman and colleagues (1991) did not demonstrate decrements for all ages, and results differed for two of the tests; Eskenazi and Trupin (1995) did not find a dose–response relationship. Results for the three studies (Denson, Nanson, and McWatters, 1975; Weitzman et al., 1992; Eskenazi and Trupin, 1995) examining postnatal ETS exposure and children's behavior are also conflicting. However, Weitzman and colleagues did demonstrate significant, dose-related associations between most categories of postnatal maternal smoking and a behavior problem index.

Cancers

Table 10-6 lists selected studies on ETS and childhood cancers. Due to the lack of distinction between true ETS exposure and maternal smoking during pregnancy, only studies associating paternal smoking and cancers are listed. The findings of these studies may be affected by confounding due to maternal smoking during pregnancy.

Brain Tumors The association between ETS and brain tumors in children is biologically plausible due to the findings of endogenously formed N-nitroso precursors found in ETS; however, this association has yet to be demonstrated in adults. Associations between paternal smoking and risk of brain tumors were demonstrated in four studies (Preston-Martin et al., 1982; Howe et al., 1989; John, Savitz, and Sandler, 1991; McCredie, Maisonneuve, and Boyle, 1994), with odds ratios ranging from 1.4 to 2.2 and with

TABLE 10-6 Studies Investigating ETS and Childhood Cancers, Using Paternal Smoking as a Surrogate of ETS

Study Reference	Location	Outcome Assessed	Exposure	Exposure Ascertainment	Participants	OR
Preston-Martin et al. (1982)	United States (Los Angeles County)	Brain tumor	Paternal smoking during pregnancy	Interview	209 cases 209 controls	1.5 ($p < 0.05$)
Howe et al. (1989)	Canada (southern Ontario)	Brain tumor	Paternal smoking during pregnancy	Interview	74 cases 132 controls	1.1
Kuijten et al. (1990)	United States (Pennsylvania, New Jersey, Delaware)	Astrocytoma	Paternal smoking during pregnancy	Interview	163 cases 163 controls	0.8
John et al. (1991)		Brain tumor	Paternal smoking alone		48 cases 196 controls	1.9 (0.9, 4.2)
Gold et al. (1993)	United State (SEER)	Brain tumor	Paternal smoking alone	Interviews	361 cases 1083 controls	0.9
McCredie et al. (1994)	Australia (New South Wales)	Brain tumor	Paternal smoking during pregnancy	Interviews	82 cases 164 controls	2.2
Magnani et al. (1990)	Italy	Leukemia	Paternal smoking during pregnancy		73 cases 196 controls	1.7 (0.7, 3.8)
John et al. (1991)		Leukemia	Paternal smoking during pregnancy		187 cases 187 controls	No association
Severson et al. (1993)		Leukemia	Paternal smoking during pregnancy		22 cases 307 controls	0.9 (0.3, 2.1)
Magnani et al. (1990)		Non-Hodgkins lymphoma	Paternal smoking during pregnancy		19 cases	6.7 (1.0, 43.4)
John et al. (1991)		Lymphoma	Paternal smoking during pregnancy		26 cases	1.9 (0.7, 4.8)

statistically significant results in two of the studies (Preston-Martin et al., 1982; McCredie, Maisonneuve, and Boyle, 1994).

Leukemia In animal studies, leukemia can be induced by transplacentally-acting carcinogens found in tobacco smoke and benzene, as a component of ETS is a leukemogen. The eight studies (Pershagen, Ericson, and Otterblad-Olausson, 1992; van Steensel-Moll et al., 1985; Stjernfeldt et al., 1986; McKinney et al., 1987; Buckley et al., 1986; Magnani et al., 1990; John, Savitz, and Sandler, 1991; Severson et al., 1993) on parental smoking and the risk of leukemia in children are conflicting. The only cohort study conducted did not demonstrate an association. Furthermore only two out of seven case-control studies demonstrated a positive association. These studies have been limited by not distinguishing between acute lymphocytic leukemia (ALL) and non-ALL and the lack of information on the patient's age of diagnosis. At the present time a positive association between ETS and leukemia cannot be supported.

Lymphomas Six studies (Buckley et al., 1986; Stjernfeldt et al., 1986; Magnani et al., 1990; McKinney et al., 1987; John, Savitz, and Sandler, 1991; Pershagen, Ericson, and Otterblad-Olausson, 1992) have been conducted on ETS exposure and the risk of lymphomas and non-Hodgkin's lymphomas. While small increases in risk were observed, the data do not support a conclusion at this time.

Other Cancers ETS exposure has also been assessed as a risk factor for neuroblastoma, germ cell tumors, bone and soft tissue sarcomas, and Wilm's tumor of the kidney. While it has been established that risk for neuroblastoma occurs through ETS exposure in utero, and a small increase in relative risk for neuroblastoma due to paternal smoking during pregnancy has been demonstrated (Kramer et al., 1987), more studies are needed. Several studies have also attempted to assess associations between ETS and germ cell tumors (McKinney et al., 1987), and also bone and soft-tissue sarcomas (Grufferman et al., 1982; McKinney et al., 1987; Hartley et al., 1988; Magnani et al., 1990). Lastly, active smoking is an established risk factor for cancers of the kidney and renal pelvis in adults, and animal studies have suggested that nitrosamines may have an etiologic role in these cancers. However, conclusive studies associating ETS with Wilm's tumor of the kidney in children have not yet been conducted.

Lower Respiratory Tract Illnesses in Childhood

Studies of involuntary smoking and lower respiratory illnesses in childhood, including bronchitis and pneumonia, provided some of the earliest evidence on adverse effects of ETS (Harlap and Davies, 1974; Colley, Holland, and Corkhill, 1974). Presumably this association represents an increase in frequency or severity of illnesses that are infectious in etiology and not a direct response of the lung to toxic components of ETS. Investigations conducted throughout the world have demonstrated an increased risk of lower respiratory tract illness in infants with smoking parents (Strachan and Cook, 1997). These studies indicate a significantly increased frequency of bronchitis and pneumonia during the first year of life of children with smoking parents. Strachan and Cook (1997) report a quantitative review of this information, combining data from 39 studies. Overall, there was an approximate 50% increase in illness risk if either parent smoked, with the odds ratio for maternal smoking being somewhat higher at 1.72 (95% confidence interval, CI: 1.55, 1.91). Although the health outcome measures have varied somewhat among the studies, the relative risks associated with involuntary smoking were similar, and dose–response relationships with extent of parental smoking were demonstrable. Although most of the studies have shown that maternal smoking rather than paternal smoking underlies the increased risk of parental smoking, studies from China show that paternal smoking alone can increase incidence of lower respiratory illness (Yue Chen, Wan-Xian, and Shunzhang, 1986; Strachan and Cook, 1997). In these studies an effect of passive smoking was not readily identified after the first year of life. During the first year of life, the strength of its effect may reflect higher exposures consequent to the time-activity patterns of young infants, which place them in close proximity to cigarettes smoked by their mothers.

Respiratory Symptoms and Illness in Children

Data from numerous surveys demonstrate a greater frequency of the most common respiratory symptoms: cough, phlegm, and wheeze in the children of smokers (DHHS, 1986; Cal EPA, 1997; Cook and Strachan, 1997). In these studies the subjects have generally been schoolchildren, and the effects of parental smoking have been examined. Thus the less prominent effects of passive smoking, in comparison with the studies of lower respiratory illness in infants, may reflect lower exposures to ETS by older children who spend less time with their parents.

By the mid-1980s results from several large studies provided convincing evidence that involuntary exposure to ETS increases the occurrence of cough and phlegm in the children of smokers, although earlier data from smaller studies had been ambiguous. In a study of 10,000 schoolchildren in six U.S. communities, smoking by parents increased the frequency of persistent cough in their children by about 30% (Ware, Dockery, and Spiro III, 1984). The effect of parental smoking was derived primarily from smoking by the mother. Charlton (1984) conducted a survey on cigarette smoking that included 15,709 English children aged 8 to 19 years. In the nonsmoking children, the prevalence of frequent cough was significantly higher if either the father or the mother smoked. For the symptom of chronic wheeze, the preponderance of the early evidence also indicated an excess associated with involuntary smoking. In a survey of 650 schoolchildren in Boston, one of the first studies on this association, persistent wheezing was the most frequent symptom (Weiss et al., 1980); the prevalence of persistent wheezing increased significantly as the number of smoking parents increased. In the large study of children in six U.S. communities, the prevalence of persistent wheezing during the previous year was significantly increased if the mother smoked (Ware, Dockery, and Spiros III, 1984).

Cook and Strachan (1997) conducted a quantitative summary of the relevant studies, including 41 of wheeze, 34 of chronic cough, 7 of chronic phlegm, and 6 of breathlessness. Overall, this synthesis indicates increased risk for respiratory symptoms for children whose parents smoke (Table 10-7) (Cook and Strachan, 1997). There was even increased risk for breathlessness (OR = 1.31; 95% CI = 1.08, 1.59). Having both parents smoke was associated with the highest levels of risk.

Childhood Asthma

Although involuntary exposure to tobacco smoke has been associated with the symptom of wheeze, evidence for association of involuntary smoking with childhood asthma was initially conflicting. Exposure to ETS might cause asthma as a long-term consequence of the increased occurrence of lower respiratory infection in early childhood or through other pathophysiological mechanisms including inflammation of the respiratory epithelium (Samet, Tager, and Speizer, 1983; Tager, 1988). The effect of ETS may also reflect, in part, the consequences of in utero exposure. Assessment of airways responsiveness shortly after birth has shown that infants whose mothers smoke during pregnancy have increased airways responsiveness compared with those whose mothers do not smoke (Young et al., 1991). Maternal smoking during pregnancy also reduced ventilatory function measured

TABLE 10-7 Asthma and Respiratory Symptoms: Summary of Pooled Random Effects Odds Ratios with 95% Confidence Intervals

	Either Parent Smokes			One Parent Smokes			Both Parents Smoke			Mother Only Smokes			Father Only Smokes		
	OR	95%CI	(*n*)	OR	95%CI	(*n*)	OR	95%CI	(*n*)	OR	95%CI	(*n*)	OR	95%CI	(*n*)
Asthma	1.21	1.10–1.34	(21)[c]	1.04	0.78–1.38	(6)	1.50	1.29–1.73	(8)	1.36	1.20–1.55	(11)	1.07	0.92–1.24	(9)
Wheeze[a]	1.24	1.17–1.31	(30)[c]	1.18	1.08–1.29	(21)	1.47	1.14–1.90	(11)	1.28	1.19–1.38	(18)[d]	1.14	1.06–1.23	(10)
Cough	1.40	1.27–1.53	(30)[c]	1.29	1.11–1.51	(15)	1.67	1.48–1.89	(16)	1.40	1.20–16.4	(14)[d]	1.21	1.09–1.34	(9)
Phlegm[b]	1.35	1.13–1.62	(6)	1.25	0.97–1.63	(5)	1.46	1.04–2.05	(5)						
Breathlessness[b]	1.31	1.08–1.59	(6)												

Source: Cook and Strachan (1997).

Note: Number of studies in parentheses.

[a] Excluding EC study, in which the pooled odds ratio was 1.20.

[b] Data for phlegm and breathlessness restricted as several comparisons are based on fewer than five studies.

[c] Two age groups for reference 80 included as separate studies.

[d] Reference 82 included as three separate studies.

shortly after birth (Hanrahan et al., 1992). These observations suggest that in utero exposures from maternal smoking may affect lung development, perhaps reducing relative airways size.

While the underlying mechanisms remain to be identified, the epidemiologic evidence linking ETS exposure and childhood asthma is mounting (Cal EPA, 1997; Cook and Strachan, 1997). The synthesis by Cook and Strachan (1997) shows a significant excess of childhood asthma if both parents or the mother smoke (Table 10-7).

Evidence also indicates that involuntary smoking worsens the status of those with asthma. The possibility that ETS adversely affects children with asthma was described as early as 1950 in a case report entitled "Bronchial Asthma due to Allergy to Tobacco Smoke in an Infant" (Rosen and Levy, 1950). More recently Murray and Morrison (1986; 1989) evaluated asthmatic children followed in a clinic. Level of lung function, symptom frequency, and responsiveness to inhaled histamines were adversely affected by maternal smoking. Population studies have also shown increased airways responsiveness for ETS-exposed children with asthma (O'Connor et al., 1987; Martinez et al., 1988). The increased level of airway responsiveness associated with ETS exposure would be expected to increase the clinical severity of asthma. In this regard exposure to smoking in the home has been shown to increase the number of emergency room visits made by asthmatic children (Evans et al., 1987). Asthmatic children with smoking mothers are more likely to use asthma medications (Weitzman et al., 1990), a finding that confirms the clinically significant effects of ETS on children with asthma. Guidelines for the management of asthma all urge reduction of ETS exposure at home (DHHS, 1997).

Lung Growth and Development

On the basis of the primarily cross-sectional data available at the time, the 1984 report of the Surgeon General (DHHS, 1984) concluded that the children of smoking parents in comparison with those of nonsmokers had small reductions of lung function, but the long-term consequences of these changes were regarded as unknown. In the two years between the 1984 and the 1986 reports, sufficient longitudinal evidence was accumulated to support the conclusion in the 1986 report (DHHS, 1986b) that involuntary smoking reduces the rate of lung function growth during childhood. Further cross-sectional studies have continued generally to confirm the evidence reviewed in the 1984 report of the Surgeon General (Burchfiel III, 1984; Tashkin et al., 1984; Tsimoyianis et al., 1987; Spengler and Ferris Jr., 1985), although not all studies have shown adverse effects of involuntary smoking on the lung function of children (Hosein and Corey, 1984; Lebowitz, 1984).

The effects of involuntary smoking on lung growth have been demonstrated in three separate major longitudinal studies with supporting findings from other less extensive studies (Samet and Lange, 1996). Based on cross-sectional data from children in East Boston, Massachusetts, Hosein, Mitchell, and Bouhuys (1977) reported that the level of FEF_{25-75}, a spirometric flow rate sensitive to subtle effects on airways and parenchymal function, declined with an increasing number of smoking parents in the household. In 1983 the investigative group of Tager and coworkers reported the results obtained on follow-up of these children over a 7 year period (see Tager et al., 1983). Using a multivariate technique, the investigators showed that both maternal smoking and active smoking by the child reduced the growth rate of the FEV_1. Lifelong exposure of a child to a smoking mother was estimated to reduce growth of the FEV_1 by 10.7%, 9.5%, and 7.0% after 1, 2, and 5 years of follow-up, respectively. Findings with additional follow-up were similar (Tager et al., 1985).

In 1983 the National Heart, Lung, and Blood Institute held a workshop on the respiratory effects of involuntary smoking. At that time adverse effects of parental smoking on children's lung function had been found in the East Boston study but not in another cohort study in Tucson, Arizona, that used similar methods for data collection. Subsequently two parallel analyses of data from these two cohort studies instigated as a result of that workshop have been reported (Tager et al., 1987; Lebowitz and Holberg, 1988). Both analyses showed that an adverse effect of parental smoking on lung growth could be demonstrated in East Boston but not in Tucson when the same analytical techniques were applied to the two data sets. The differing results could reflect higher exposures in East Boston related to the type of housing and the pattern of smoking or to other unmeasured differences in the populations.

Longitudinal data from the study of air pollution in six U.S. cities also showed reduced growth of the FEV_1 in children whose mothers smoked cigarettes (Berkey, Ware, and Dockery, 1986). The growth rate of the FEV_1 from ages 6 through 10 years was calculated for 7834 white children. The findings of a statistical analysis were that from ages 6 through 10 years, FEV_1 growth rate was reduced by 0.17% per pack of cigarettes smoked daily by the mother. This effect was somewhat smaller than that reported by Tager et al. (1983), although, if it is extrapolated to age 20 years, a cumulative effect of 2.8% is predicted. In the most recent analysis of these data, Wang and colleagues (1994) modeled exposures in a time-dependent fashion, classifying exposure during the first five years of life and cumulative exposure up to the year before follow-up. Current maternal smoking was found to affect lung growth.

Burchfiel and coworkers (Burchfiel III, 1984; Burchfiel et al., 1986) examined the effects of parental smoking on 15 year lung function change in subjects in the Tecumseh study, who had been enrolled at ages 10 through 19 years. In the female subjects who remained nonsmokers across the follow-up period, parental smoking did not affect lung function change. In nonsmoking males, parental smoking reduced the growth of the FEV_1, FVC, and v_{max50}, although the sample size was limited and the effects were not statistically significant. For the FEV_1 in males, the analysis estimated 7.4% and 9.4% reductions in 15 year growth associated with one or two smoking parents, respectively.

ETS and Middle Ear Disease in Children

Otitis media is one of the most frequent diseases diagnosed in children at outpatient facilities. Otitis media occurs as a result of dysfunction in the eustachian tube; serious, otitis media results when serous fluid effuses into the middle ear, and acute otitis media results when the serous fluid effused into the middle ear becomes infected. All stages lead to varying degrees of hearing loss.

We have identified 21 studies (Table 10-8) on the association between ETS and otitis media in children. ETS exposure in these studies is mostly assessed by questionnaire or interview of the parents. Two studies assessed ETS exposure objectively through the use of biomarkers (serum or salivary cotinine measurements in the children). Outcomes assessed in these 21 studies vary from acute, persistent, and recurrent otitis media or middle ear effusion, to consequences of otitis media such as hearing loss and ear surgery. In general, these studies support a positive association between ETS and middle ear disease.

There are four biologically plausible mechanisms by which ETS could lead to middle ear disease in children. First, ETS exposure could lead to decreased mucociliary clearance, increasing possible risk of dysfunction in the eustachian tube. Second, ETS may decrease eustachian tube patency due to adenoidal hyperplasia, a known risk factor for otitis media. Third, ETS may also decrease patency as a result of ETS-induced mucosal swelling. Fourth, ETS could decrease patency and mucociliary clearance by causing more frequent viral upper respiratory infections.

TABLE 10-8 Studies of Middle Ear Disease in Children

Source	Location	Outcome	Exposure Measurement	Age of Children	RR	95% CI
			Cohort			
Iversen (1985)	Denmark	MEE[a]				
Tainio (1988)	Finland	>3 episodes of OM[b]	Questionnaire	0–7 years	Increase	$p < 0.05$
Teele (1989)	United States (Boston)	Acute OM	Questionnaire	0–2.5 years	1.7	1.1, 2.7
Etzel et al. (1992)		Incident OM with effusion	Questionnaire	0–1 year	Increase	
Ponka (1991)	Finland (Helsinki)	OM	Serum cotinine	0–5.3 years	1.4 (idr)	1.2, 1.6
Collet (1995)	Canada	Recurrent OM	Interview		No association	
Ey (1995)	United States	Recurrent OM	Questionnaire	0–4 years	1.8	1.1, 3.0
			Questionnaire	0–1 year	1.8	1.0, 3.1
			Case control			
Kraemer (1983)		Persistent MEE	Interview		2.8	1.1, 7.0
Black (1985)		Ear surgery for secretory OM	Questionnaire		1.6	1.0, 2.6
Pukander (1985)	Finland	Acute OM		2–3 years	Trend	$p < 0.05$
Fleming (1987)	United States (Georgia)	OM	Interview	< 5 years	1.1	$p = 0.82$
Hinton (1989)		Ear surgery	Medical records	2–11 years	Trend	$p = 0.06$
Takasaka (1990)		OM			No association	
Kallail (1987)	United States (Kansas)	Hearing loss			No association	
Hinton (1988)		MEE	Questionnaire	1–11 years		
Zielhius (1989)		Incident OM with MEE	Interview	2–4 years	1.1	$p = 0.6$
Barr (1991)		Ear surgery		1.5–11.5 years	No association	
Green (1991)	West Germany	ENT clinic for ear pain and Hearing loss	Questionnaire	1.5–8 years	1.9	1.2, 2.9
Kitchens (1995)	United States	MEE, recurrent OM or adhesive OM	Questionnaire	≤ 3 years	1.7	$p = 0.05$
			Cross sectional			
Strachan (1989)	Scotland (Edinburgh)	MEE	Serum continine	6.5–7.5 years	1.3 trend	1.0, 1.3
Ra (1992)		Hearing loss		10 months old		$p < 0.05$ 4.9 times

[a] MEE = middle ear effusion
[b] OM = otitis media

Epidemiologic Findings on Ear Disease

There have been 7 cohort studies, 2 cross-sectional, and 12 case-control studies (Table 10-8) conducted to determine the association between ETS and middle ear disease. Outcomes assessed vary from middle ear effusion in one study to different diagnostic categories of otitis media, such as recurrent episodes of otitis media, acute otitis media, and incident otitis media. Disease consequences such as ear surgery and hearing loss were also assessed. Exposure to ETS was usually assessed with a questionnaire or by interview and in some studies, ETS exposure was measured with serum cotinine assay (Etzel et al., 1992; Strachan, Jarvis, and Feyerabend, 1989).

Otitis Media Six of the seven cohort studies demonstrated an increase in risk for otitis media or middle ear effusion; these studies were also cohorts that included children who were followed from birth to one or two years of age, therefore including the peak age of risk in which children are most likely to suffer from otitis media. Teele, Klein, and Rosner (1989) demonstrated an increase in risk for otitis media in children less than one year of age. Etzel and colleagues (1992) also demonstrated an increase in risk (RR:1.4; 95% CI: 1.2, 1.6) for incident otitis media with effusion for their cohort of children 0.5 to 3 years of age, using serum cotinine as a measure of ETS exposure. The study of Ponka (1991) was the only cohort study not showing an increase in risk for otitis media associated with ETS. However, this study has a potential limitation, since the otitis media outcome was not objectively measured but was assessed by parental reports. Collet et al. (1995), Ey et al. (1995), and Tainio et al. (1988) all measured recurrent episodes of otitis media and demonstrated increased risk for recurrent otitis media associated with ETS, reporting relative risks of 1.8 (95% CI: 1.1, 3.0), 1.8 (95% CI: 1.0, 3.1), and 1.7 (95% CI: 1.1, 2.7), respectively.

Results from case-control studies were inconsistent, with Pukander et al. (1985) demonstrating a significant positive trend but other studies not finding significant associations (Fleming et al., 1987; Takasaka, 1990; Zielhius et al., 1989).

Middle Ear Effusion The only study assessing middle ear effusion as an outcome was that of Iversen et al. (1985); a significant increase in risk for middle ear effusion with ETS was demonstrated. The case-control studies consistently demonstrated an increased risk for middle ear effusion associated with ETS. Kraemer et al. (1983) and Kitchens (1995) both demonstrated increased risk for middle ear effusion with ETS, with odds ratios of 2.8 (95% CI: 1.1, 7.0) and 1.7 ($p < 0.05$), respectively. Hinton and Buckley (1988) demonstrated a positive increase and trend ($p = 0.06$) for middle ear effusion as a result of ETS exposure.

Consequences of Middle Ear Disease Only one of three case-control studies demonstrated an increase in risk for ear surgery due to ETS-induced otitis media. Black (1985) demonstrated an odds ratio of 1.6 (95% CI: 1.0, 2.6) for ear surgery, Hinton and Buckley (1988) demonstrated a positive trend, and Barr and Coatesworth (1991) found no association.

Two case-control studies assessed the association between ETS and hearing loss due to middle ear disease. Green and Cooper (1991) demonstrated an increase in risk with an odds ratio of 1.9 (95% CI: 1.2, 2.9) for hearing loss. While Kallail, Rainbolt, and Bruntzel (1987) did not demonstrate an association, this study suffers from a major limitation; cases and controls were not subject to the same screening procedure. Ra's cross-sectional study (Ra, 1992) demonstrated that children exposed to ETS were 4.9 times more likely to suffer from hearing loss associated with middle ear diseases.

Conclusion

Issues of concern in these studies include possible misclassification of exposure or outcome. Exposure measured through questionnaire may not fully represent the extent of smoking behavior during pregnancy and after pregnancy. However, studies using objective measures of exposure such as salivary and serum cotinine measurements both demonstrated increase in risk for otitis media. Diagnosis of otitis media is also subject to misclassification, since it is subject to variation not only between different clinics but over time. However, while case-control studies are subject to screening differences and uses of different medical services in otitis media diagnosis, cohort studies reduce potential outcome misclassification and consistently demonstrated an increase in risk for otitis media.

Positive associations between ETS and otitis media have been consistently demonstrated in cohort studies but not as consistently in the case-control studies. This difference may have arisen because the cohort studies include children from birth to age 2 years, the peak age of risk for middle ear disease. The case-control studies, on the other hand, have been directed at older children who are not at peak risk for otitis media. Regardless of study type, however, increase in risk for middle ear disease is demonstrated when the outcome assessed is recurring episodes of middle ear effusion or otitis media, versus incident or single episodes of otitis media. In a 1997 meta-analysis Cook and Strachan (1997) found a pooled odds ratio of 1.48 (95% CI: 1.08, 2.04) for recurrent otitis media if either parent smoked, 1.38 (95% CI: 1.23, 1.55) for middle ear effusions, and 1.21 (95% CI: 0.95, 1.53) for outpatient or inpatient care for chronic otitis media or "glue ear."

The U.S. Surgeon General's Office (DHHS, 1986b), the National Research Council (NRC, 1986a), and the U.S. Environmental Protection Agency (EPA, 1992) have all reviewed the literature on ETS and otitis media, and they have concluded that there is an association between ETS exposure and otitis media in children. The evidence to date supports a causal relationship.

HEALTH EFFECTS OF INVOLUNTARY SMOKING IN ADULTS

Lung Cancer

In 1981 reports were published from Japan (Hirayama, 1981) and from Greece (Trichopoulos et al., 1981) that indicated increased lung cancer risk in nonsmoking women married to cigarette smokers. Subsequently this controversial association has been examined in investigations conducted in the United States and other countries. The association of involuntary smoking with lung cancer derives biological plausibility from the presence of carcinogens in sidestream smoke and the lack of a documented threshold dose for respiratory carcinogens in active smokers (DHHS, 1982; IARC, 1986). Moreover, genotoxic activity had been demonstrated for many components of ETS (Lofroth, 1989; Claxton et al., 1989; Weiss, 1989), although several small studies have not found cytogenetic effects in passive smokers (Sorsa et al., 1985; Husgafvel-Pursiainen et al., 1987; Sorsa et al., 1989). Experimental exposure of nonsmokers to ETS leads to their excreting NNAL, a tobacco-specific carcinogen, in their urine (Hecht et al., 1993). Nonsmokers exposed to ETS also have increased concentrations of adducts of tobacco-related carcinogens (Maclure et al., 1989; Crawford et al., 1994).

Time trends of lung cancer mortality in nonsmokers have been examined with the rationale that temporally increasing exposure to ETS should be paralleled by increasing mortality rates (Enstrom, 1979; Garfinkel, 1981). These data provide only indirect evidence on the lung cancer risk associated with involuntary exposure to tobacco smoke. Epidemiologists have directly tested the association between lung cancer and involuntary smoking utilizing conventional designs: the case-control and cohort studies. In a case-control study, the exposures of nonsmoking persons with lung cancer to ETS are compared to those of an appropriate control group. In a cohort study, the occurrence of lung cancer over time in nonsmokers is assessed in relation to involuntary tobacco smoke exposure. The results of both study designs may be affected by inaccurate assessment of exposure to ETS, by inaccurate information on personal smoking habits that leads to classification of smokers as nonsmokers, by failure to assess and control for potential confounding factors, and by the misdiagnosis of a cancer at another site as a primary cancer of the lung.

Methodological investigations suggest that accurate information can be obtained by interview in an epidemiological study on the smoking habits of a spouse (i.e., never or ever smoker) (Pron et al., 1988; Coultas, Peake, and Samet, 1989; Cummings et al., 1989). However, information concerning quantitative aspects of the spouse's smoking is reported with less accuracy. Misclassification of current or former smokers as never-smokers may introduce a positive bias because of the concordance of spouse smoking habits (Lee, 1988). The extent to which this bias explains the numerous reports of association between spouse smoking and lung cancer has been controversial (Wald et al., 1986; Lee, 1988; EPA, 1992).

Use of spouse smoking alone to represent exposure to ETS does not cover exposures outside of the home (Friedman, Petitti, and Bawol, 1983), nor necessarily all exposure inside the home. The International Agency for Research on Cancer (IARC) has conducted a 13-center study to assess the contribution of the home and work environments to exposures of nonsmoking women to ETS (Saracci and Riboli, 1989). Overall, the data show that some women married to smokers receive little exposure at home and that the number of cigarettes smoked per day by the husband is only moderately correlated with "actual" exposure. The study shows a widely varying proportion of women exposed to ETS among the centers.

A U.S. study examined the contribution of spouse smoking to total exposure to ETS received at home (Sandler et al., 1989). Using 1963 data from the Washington County, Maryland, study, Sandler and colleagues found that for nonsmoking women, spouse smoking contributed 88% of the exposure, whereas for nonsmoking men, spouse smoking contributed 62% of the exposure.

In some countries, including the United States, smoking prevalence varies markedly with indicators of income and education, more recently tending to rise sharply with decreasing educational level and income (DHHS, 1989). In general, exposure to ETS follows a similar trend, and critics of the findings on ETS and lung cancer have argued that uncontrolled confounding by lifestyle, occupation, or other factors may explain the association. In fact, current data for the United States do indicate a generally less healthy lifestyle in those with greater ETS exposure (Matanoski et al., 1995). However, other than a few occupational exposures at high levels, as well as indoor radon, risk factors for lung cancer in never-smokers that might confound the ETS association cannot be proffered and the relevance to past studies of these current associations of potential confounders with ETS exposure is uncertain.

The first major studies on ETS and lung cancer were reported in 1981. Hirayama's (1981) early report was based on a prospective cohort study of 91,540 nonsmoking women in Japan. Standardized mortality ratios (SMRs) for lung cancer increased significantly with the amount smoked by the husbands. The findings could not be explained by confounding factors and were unchanged when follow-up of the study group was extended (Hirayama, 1984). Based on the same cohort, Hirayama also reported significantly increased risk for nonsmoking men married to wives smoking one to 19 cigarettes and 20 or more cigarettes daily (Hirayama, 1984). In 1981 Trichopoulos and colleagues also reported increased lung cancer risk in nonsmoking women married to cigarette smokers (see Trichopoulos et al., 1981). These investigators conducted a case-control study in Athens, Greece, which included cases with a diagnosis other than for orthopedic disorders. The positive findings reported in 1981 were unchanged with subsequent expansion of the study population (Trichopoulos, Kalandidi, and Sparros, 1983).

By 1986 the evidence had mounted, and three reports published in that year concluded that ETS was a cause of lung cancer. The International Agency for Research on Cancer of the World Health Organization (IARC, 1986) concluded that "passive smoking gives rise to some risk of cancer." In its monograph on tobacco smoking, the agency supported this conclusion on the basis of the characteristics of sidestream and mainstream smoke, the absorption of tobacco smoke materials during involuntary smoking, and the nature of dose–response relationships for carcinogenesis. In the same year the National Research Council (NRC, 1986a) and the U.S. Surgeon General (DHHS, 1986b) also concluded that involuntary smoking increases the incidence of lung cancer in nonsmokers. In reaching this conclusion, the National Research Council (NRC, 1986a) cited the biological plausibility of the association between exposure to ETS and lung cancer and the supporting epidemiological evidence. Based on a pooled analysis of the epidemiological data adjusted for bias, the report concluded that the best estimate for the excess risk of lung cancer in nonsmokers married to smokers was 25%. The 1986 report of the Surgeon General (DHHS, 1986b) characterized involuntary smoking as a cause of lung cancer in nonsmokers. This conclusion was based on the extensive information already available on the carcinogenicity of active smoking, on the qualitative similarities between ETS and mainstream smoke, and on the epidemiological data on involuntary smoking.

In 1992 the U.S. Environmental Protection Agency (EPA, 1992) published its risk assessment of ETS as a carcinogen. The agency's evaluation drew on the toxicologic evidence on ETS and the extensive literature on active smoking. A meta-analysis of the 31 studies published up to that time was central in the decision to classify ETS as a class A carcinogen — namely a known human carcinogen. The meta-analysis considered the data from the epidemiologic studies by tiers of study quality and location and used an adjustment method for misclassification of smokers as never-smokers. Overall, the analysis found a significantly increased risk of lung cancer in never-smoking women married to smoking men; for the studies conducted in the United States, the estimated relative risk was 1.19 (90% CI: 1.04, 1.35). Critics of the report have raised a number of concerns including the use of meta-analysis, reliance of 90% rather than 95% confidence intervals, uncontrolled confounding, and information bias. The report, however, was endorsed by the Agency's Science Advisory Board, and its conclusion is fully consistent with the 1986 reports.

Subsequent to the 1992 risk assessment, several additional studies in the United States have been reported (Brownson et al., 1992; Fontham et al., 1994; Kabat, Stellman, and Wynder, 1995; Cardenas et al., 1997). The multicenter study of Fontham and colleagues is the largest report to date, with 651 cases and 1253 controls. It shows a significant increase in overall relative risk (OR : 1.26; 95% CI : 1.04, 1.54). There was also a significant risk associated with occupational exposure to ETS.

Findings of an autopsy study conducted in Greece have further strengthened the plausibility of the lung cancer ETS connection. Trichopoulos and colleagues (1992) examined autopsy lung specimens from 400 persons, 35 years of age and older, in order to assess airways changes. Epithelial lesions were more common in nonsmokers married to smokers than in nonsmokers married to nonsmokers.

A more recent meta-analysis (Hackshaw, Law, and Wald, 1997) included 37 published studies. The excess risk of lung cancer for smokers married to nonsmokers was estimated at 24% (95% CI: 13%, 36%). The adjustment for potential bias and confounding by diet did not alter the estimate. This meta-analysis has supported the recent conclusion of the

U.K. Scientific Committee on Tobacco and Health (Scientific Committee on Tobacco and Health and HSMO, 1998) that ETS is a cause of lung cancer.

The extent of the lung cancer hazard associated with involuntary smoking in the United States and in other countries remains subject to some uncertainty, however (DHHS, 1986b; Weiss, 1986). The epidemiological studies provide varying and imprecise measures of risk, and exposures have not been characterized for large and representative population samples. Nevertheless, risk estimation procedures have been used to describe the lung cancer risk associated with involuntary smoking, but assumptions and simplifications must be made in order to use this method. The estimates of lung cancer deaths attributable to passive smoking have received widespread media attention and have figured prominently in the evolution of public policy on passive smoking.

Repace and Lowrey (1990) reviewed the risk assessments of lung cancer and passive smoking and estimated the numbers of lung cancer cases among U.S. nonsmokers that could be attributed to passive smoking. They provide nine estimates, covering both never-smokers and former smokers; the estimates ranged from 58 to 8124 lung cancer deaths for the year 1988, with a mean of 4500 or 5000 excluding the lowest estimate of 58. The bases for the individual estimates included the comparative dosimetry of tobacco smoke in smokers and nonsmokers using presumed inhaled dose or levels of nicotine or cotinine, the epidemiological evidence, and modeling approaches. A 1992 estimate by the Environmental Protection Agency, based on the epidemiologic data, was about 3000, including 1500 and 500 deaths in never-smoking women and men, respectively, and about 100 in long-term former smokers of both sexes.

More recently Repace and colleagues (1998) developed a model of risk to workers of lung cancer and heart disease arising from ETS exposure. The pharmacokinetic model incorporated nicotine as an indicator of exposure and cotinine as a measure of dose in order to estimate the risks. The model estimated that 400 lung cancer deaths occur annually from workplace exposure at a prevalence of 28% smoking in the workplace.

These calculations illustrate that passive smoking must be considered an important cause of lung cancer death from a public health perspective, since exposure is involuntary and not subject to control. The specific risk assessments require assumptions concerning the extent and degree of exposure to ETS, exposure-response relationships, and the lifetime expression of the excess risk associated with passive smoking at different ages. Moreover the calculations do not consider the potential contributions of other exposures, such as occupational agents and indoor radon. The current decline in the prevalence of active smoking and the implementation of strong clean indoor air policies will reduce the relevance of estimates based on past patterns of smoking behavior.

Other Cancers

In adults, involuntary smoking has been linked to a generally increased risk of malignancy and to excess risk at specific sites. Miller (1984) interviewed surviving relatives of 537 deceased nonsmoking women in western Pennsylvania concerning the smoking habits of their husbands. A significantly increased risk of cancer death (OR: 1.94; $p < 0.05$) was found in women who were married to smokers and also not employed outside the home. The large number of potential subjects who were not interviewed and the possibility of information bias detract from this report.

Sandler and colleagues (Sandler, Everson, and Wilcox, 1985; Sandler et al., 1985; Sandler, Wilcox, and Everson, 1985) conducted a case-control study on the effects of exposure to ETS during childhood and adulthood on the risk of cancer. The 518 cases included cancers of all types other than basal cell cancer of the skin; the cases and the matched controls were between the ages of 15 and 59 years. For all sites combined, significantly increased risk was found for parental smoking (crude OR : 1.6); and for marriage to a smoking spouse (crude OR : = 1.5); the effects of these two exposures were independent (Sandler, Wilcox, and Everson, 1985). Significant associations were also found for some individual sites: For childhood exposure (Sandler et al., 1985), maternal and paternal smoking increased the risk of hematopoietic malignancy, and for adulthood exposure (Sandler, Everson, and Wilcox, 1985), spouse's smoking increased the risk for cancers of the female breast, female genital system, and the endocrine system. The findings are primarily hypothesis-generating and require replication. In a case-control study, such as those reported by Sandler et al. (1985), information on exposure to ETS may be affected by information bias.

Other studies provide data on passive smoking and cancers of diverse sites. Hirayama (1984) has reported significantly increased mortality from nasal sinus cancers and from brain tumors in nonsmoking women married to smokers in the Japanese cohort. In a case-control study of bladder cancer, involuntary smoke exposure at home and at work did not increase risk (Kabat, Dieck, and Wynder, 1986). Cervical cancer, which has been linked to active smoking (DHHS, 1990a), was associated with duration of involuntary smoking in a case-control study in Utah (Slattery et al., 1989). In the Washington County (Maryland) study, colorectal cancer incidence rates were significantly increased for male passive smokers but not for female passive smokers; incidence rates were significantly reduced for female active smokers (Sandler et al., 1988). This pattern of findings cannot be readily explained.

These associations of involuntary smoking with cancer at diverse nonrespiratory sites cannot be readily supported with arguments for biological plausibility. Increased risks at some of the sites, such as cancer of the nasal sinus and female breast cancer, generally have not been observed in active smokers (DHHS, 1982, 1989, DHHS, 1990b). In fact the International Agency for Research on Cancer has concluded that effects would not be produced in passive smokers that would not be produced to a larger extent in active smokers (IARC, 1986). Thus investigation of cancer sites other than the lung should be guided by the data from active smokers and by appropriate toxicological evidence. For example, the plausibility of the passive smoking with cervical cancer would be supported by the demonstration of tobacco smoke components in the cervical mucus of exposed nonsmoking women. In investigations of cancer at sites not plausibly linked to passive smoking, associations may arise by chance or by the effect of bias, prompting further but possibly unnecessary investigations.

ETS and Coronary Heart Disease

Causal associations between active smoking and fatal and nonfatal coronary heart disease (CHD) outcomes have long been demonstrated (DHHS, 1989). This increased risk of CHD morbidity and mortality has been demonstrated for younger persons and the elderly, in men and women, and in ethnically and racially diverse populations. The risk of CHD in active smokers increases with amount and duration of cigarette smoking and decreases quickly with cessation. Active cigarette smoking is considered to increase the risk of cardiovascular disease by promoting atherosclerosis, increasing the tendency to thrombosis, causing spasm of the coronary arteries, increasing the likelihood of cardiac arrhythmias, and decreasing the oxygen-carrying capacity of the blood (DHHS, 1990a). It is biologically plausible that passive smoking could also be associated with increased risk for CHD through the same mechanisms considered relevant for active smoking, although the lower exposures to smoke components of the passive smoker have raised questions regarding the relevance of the mechanisms cited for active smoking.

Biological Plausibility Glantz and Parmley (1991) have summarized the pathophysiological mechanisms by which passive smoking might increase the risk of heart disease. They suggest that passive smoking may promote atherogenesis, increase the tendency of platelets to aggregate and thereby promote thrombosis, reduce the oxygen-carrying capacity of the blood, and alter myocardial metabolism, much as for active smoking and CHD. The relevant data are presently limited in scope, but experimental models have been developed. Three separate experiments involving exposure of nonsmokers to ETS have shown that passive smoking affects measures of platelet function in the direction of increased tendency toward thrombosis (Glantz and Parmley, 1995). However, changes in these same types of assays of platelet function have not been consistently associated with active smoking (DHHS, 1990c). Glantz and Parmley also propose that carcinogenic agents such as polycyclic aromatic hydrocarbons found in tobacco smoke promote atherogenesis by effects on cell proliferation. Passive smoking may also worsen the outcome of an ischemic event in the heart; animal data have demonstrated that ETS exposure increases cardiac damage following an experimental myocardial infarction. Experiments on two species of animals (rabbits and cockerels) have demonstrated that not only does exposure to ETS at doses similar to exposure to humans accelerate the growth of atherosclerotic plaques through the increase of lipid deposits, but it also induces atherosclerosis.

In addition to its effects on platelets, passive smoke exposure affects the oxygen-carrying capacity of the blood. Even small increments, on the order of 1%, in the carboxyhemoglobin, may explain the finding that passive smoking decreases the duration of exercise of patients with angina pectoris (Allred et al., 1989). This is supported with evidence that cigarette smoking has been shown to increase levels of carbon monoxide in the spaces where ventilation is low or smoking is particularly intense (DHHS, 1986a).

Epidemiological Studies Epidemiologic data first raised concern that passive smoking may increase risk for CHD with the report of Garland and colleagues (1985) based on a cohort study in southern California. We identified 22 studies on the association between environmental tobacco smoke and cardiovascular disease (Table 10-9), including 11 cohort and 10 case-control studies, and 1 cross-sectional study. These studies assessed both fatal and nonfatal cardiovascular heart disease outcomes, and most used self-administered questionnaires to assess ETS exposure. They cover a wide range of populations, both geographically and racially. While many of the studies were conducted within the United States; studies were also conducted in Europe (Scotland, Italy, and the United Kingdom), Asia (Japan and China), South America (Argentina), and the South Pacific (Australia and New Zealand). The majority of the studies measured the effect of ETS exposure due to spousal smoking; however, some studies also assessed exposures from smoking by other household members or occurring at work or in transit. Only one study included measurement of biomarkers.

As the evidence has subsequently mounted since the 1985 report, it has been systematically reviewed by the American Heart Association (Taylor, Johnson, and Kazemi, 1992) and the California Environmental Protection Agency(Cal EPA, 1997), and also in a recent meta-analysis done for the Scientific Committee on Tobacco and Health in the United Kingdom (Law, Morris, and Wald, 1997). The topic was not addressed in the 1986 Surgeon General's report nor in the 1992 EPA risk assessment of ETS because of the limited data available when these reports were prepared.

Cohort Studies

Fatal CHD Outcomes Cohort studies assessing the association between ETS and fatal CHD outcomes have all demonstrated an increase in risk. In a cohort of nonsmoking Japanese women married to husbands who smoked, Hirayama (1984) demonstrated a modest increase in risk for death from ischemic heart disease. Hole and colleagues (1989)

TABLE 10-9 Studies Investigating ETS and CHD Outcomes

Study Reference	Location	Outcome(s) Assessed	Exposure	Participants	Combined *RR*	Men	Women	RR Adjusted for:
				Cohort				
Butler (1988 dissertation)	California (Loma Linda–Seventh Day Adventists)	Fatal CHD	Spousal (husband)	Spouse pairs: 87 female CHD deaths / 9785 nonsmoking women			1.4 (0.5, 3.8)	Age
			Household (years lived with smoker) Work (years worked with smoker)	AHSMOG 76 male CHD deaths / 1489 never-smoking men 70 CHD female deaths / 3486 never-smoking women		0: 1.0 1–10: 0.4 11+: 0.6 0: 1.0 1–10: 1.3 11+: 0.8	0: 1.0 1–10: 1.5 11+: 1.5 0: 1.0 1–10: 1.8 11+: 1.9	
Garland et al. (1985)	California (San Diego)	Fatal CHD (ICDA-8: 410.0–414.9)	Spousal (husband)	19 female CHD deaths / 695 nonsmoking women			2.7	Age, systolic blood pressure, total plasma cholesterol, obesity, years of marriage
Helsing et al. (1988)	Maryland (Washington County)	Fatal CHD (ICD-7)	Household exposure	370 male CHD deaths / 3454 men; 988 female CHD deaths / 12,348 women	1.2	1.3 (1.1,1.6) Score: 0: 1.0 1–5: 1.4* 6–12: 1.3	1.2 (1.1, 1.4) Score: 0: 1.0 1–5: 1.2 6–12: 1.3*	Age, housing quality, schooling, marital status
Hirayama (1984, 1989, 1990)	Japan	Fatal CHD	Spousal (husband)	494 female deaths / 91,540 nonsmoking women			Cigarette/day: None: 1.0 1–19: 1.0 20+: 1.3*	Husband's age, occupation
Hole et al. (1989)	Western Scotland	Nonfatal angina	Cohabitees	525 IHD deaths / 3960 men 4037 women	1.1 (0.7, 1.7)			Age, sex, social class, diastolic blood pressure, serum cholesterol, body mass index
		Fatal ischemic heart disease			2.0 (1.2, 3.4)			

TABLE 10-9 *(Continued)*

Study Reference	Location	Outcome(s) Assessed	Exposure	Participants	Combined *RR*	Men	Women	RR Adjusted for:
Humble et al. (1990)	Georgia (Evans County)	Fatal CVD (ICD8: 390–456)	Spousal (husband)	76 female CVD deaths / 185 never-smoking black women 328 never-smoking white women			1.6 (1.0, 2.6) Blacks: 1.8 (0.9, 3.7) Whites: Low SES: 1.8 High SES: 2.0	Age, blood pressure, cholesterol, body mass index
Hunt et al. (1986)	Utah	Incident fatal heart attack	Spousal (husband)	9172 spouse pairs			3.4	
Kawachi et al. (1997)	United States (Nurses' Health Study)	Incident CHD:	Home or work	152 CHD cases:			Home or work: None: 1.0 Any: 1.7* Occasional: 1.6 Regular: 1.8* Years with smoker: < 1: 1.0 1–9: 1.2 10–19: 1.5 20–29: 1.1 30 +: 1.5	Alcohol use, body mass index History of: hypertension, diabetes, hypercholesterolemia, menopausal status, hormone use, physical activity, vitamin E intake, fat intake, aspirin use, family history of CHD
		nonfatal MI		127 CHD cases			Home or work: None: 1.0 Any: 1.7 Occasional: 1.6 Regular: 1.9*	
		but fatal CHD		25 CHD cases			Home or work: None: 1.0 Any: 1.9 Occasional: 1.5 Regular: 2.6	

LeVois and Layard (1995)	United States (CPS-I and CPS II)	Fatal CHD (ICD7: 420.0–420.2	Spousal	7768 male CHD deaths/ 88,458 never-smoking men; 7133 female CHD deaths/247,412 never-smoking women		1.0 (0.9, 1.1) Cigarette/day: 1–9: 1.0 20–39: 1.0 40+: 1.0	1.1 (1.0, 1.1) Cigarette/day: 1–19: 1.0 20–39: 1.1 40+: 1.0	Age, race
	CPS-1 and II	ICD9: 410–414)		1966 male CHD deaths/ 108,772 never-smoking men; 1099 CHD female deaths/ 226,067 never-smoking women		1.0 (0.9, 1.1) Cigarette/day: 1–19: 1.4* 20–39: 1.3 40+: 1.1	1.0 (0.9, 1.1) Cigarette/day: 1–19: 1.1 20–39: 1.0 40+: 1.3	
					1.0 (0.97, 1.04) Cigarette/day: 1–19: 1.1 20–39: 1.1 40+: 1.0	1.0 (0.9, 1.0) Cigarette/day: 1–19: 1.1 20–39: 1.1 40+: 0.9	1.0 (1.0, 1.1) Cigarette/day: 1–19: 1.1 20–39: 1.1 40+: 1.0	
Steenland et al. (1996)	United States (CPS-II)	Fatal CHD (ICD-9:410–414)	Spousal	Analysis 1: 2494 male CHD deaths/ 101,227 men; 1325 female CHD deaths/ 208,372 women		1.2 (1.1, 1.4) Cigarette/day: < 20: 1.3* 20: 1.2 21–39: 1.1	1.1 (1.0, 1.3) Cigarette/day: < 20: 1.1 20: 1.1 21–39: 1.0 40+: 1.0	Age, history of heart disease, hypertension, diabetes, arthritis, body mass index, educational level, aspirin use, diuretic use, liquor consumption in men, wine intake in women, employment status, exercise, estrogen use in women
				Analysis 2: 1299 male CHD deaths/ 58,530 men; 572 CHD female deaths/ 99,821 women		1.5 (1.2, 1.8) Cigarette/day: < 20: 1.1 20: 1.1 21–39:1.1 40+: 1.3*	1.2 (0.9, 1.5) Cigarette/day: < 20: 0.8 20: 1.0 21–39: 1.2 40+: 1.2	

TABLE 10-9 ***(Continued)***

Study Reference	Location	Outcome(s) Assessed	Exposure	Participants	Combined *RR*	Men	Women	RR Adjusted for:
				Analysis 3: 1180 male CHD deaths / 54,668 men; 426 female CHD deaths / 80,549 women		1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	
						Cigarette / day: < 20: 1.4* 20: 1.2 21–39: 1.1	Cigarette / day: < 20: 1.2 20: 1.1 21–39: 1.0 40 + : 1.3	
				Analysis 4: 1751 deaths / 76,710 men; 768 deaths / 75,237 women		1.2 (1.0, 1.3)	1.1 (1.0, 1.2)	
			Home			1.0 (0.9, 1.2)	1.1 (0.8, 1.3)	
			work			1.0 (0.9, 1.1)	0.9 (0.8, 1.0)	
			elsewhere					
Svendsen et al. (1987)	United States (MRFIT: 18 cities)	Fatal CHD	Spousal (wife)	13 male CHD deaths / 56 nonfatal CHD / 1245 never-smoking men		Fatal: 2.2 (0.7, 6.9)		Age, baseline blood pressure, cholesterol, weight, drinks/week, education
		Fatal and nonfatal CHD				both: 1.6 (1.0, 2.7)		
			Coworkers			Fatal: 2.6 (0.5, 12.7) Both: 1.4 (0.8, 2.5)		Age, wives' smoking status
				Case Control				
Ciruzzi et al. (1996)	Argentina (coronary care units)	Acute myocardial infarction	Household	336 AMI cases 446 hospital controls	1.7 (1.2, 2.3)			Age, sex, education, body mass index, hyperlipidemia, family history of: diabetes, hypertension, history of CHD
					1.4 (0.9, 2.0)			
			Spousal		Cigarette / day: 1–20: 1.3 > 20: 2.4			

Dobson et al. (1991)	Australia (New South Wales)	Fatal MI or fatal CHD (WHO MONICA)	Home	183 male cases / 293 nonsmoking male controls; 160 female cases / 532 nonsmoking female controls	0.97 (0.5, 1.9)	2.5 (1.5, 4.1)	Age, history of MI
			Work	75 male cases / 205 nonsmoking male controls; 17 female cases / 197 nonsmoking female controls	1.0 (0.5, 1.8)	0.7 (0.2, 2.6)	
He et al. (1989)	People's Republic of China	Nonfatal CHD (WHO)	Spousal (husband)	34 female CHD cases 34 population 34 hospital controls		3.0 (1.3, 7.2) Cigarette / day: < 20: 2.3 > 20: 6.8	Personal history of: hypertension, hyperlipidemia, Family history of: hypertension, CHD, drinking, physical exercise
He et al. (1994)	People's Republic of China (Xian)	Nonfatal CHD	Spousal (husband) and work	59 cases 126 controls		1.2 (0.6, 2.7)	None
			Work only			1.9 (0.9, 4.0) Number of smokers: 0: 1.0 1–2: 1.2 3: 5.1 4+: 4.1	Age, history of hypertension, personality type, total cholesterol, HDL cholesterol
Jackson (1989 dissertation)	New Zealand	Acute MI (WHO MONICA)		28 male AMI cases / 123 male controls; 11 female AMI cases / 112 female controls	1.0 (0.3, 4.3)	2.7 (0.6, 13)	Age, SES
		Fatal CHD		21 male CHD deaths/ 61 male controls; 9 female CHD deaths/ 62 female controls	1.1 (0.2, 4.5)	5.8 (1.3, 48)	

TABLE 10-9 (*Continued*)

Study Reference	Location	Outcome(s) Assessed	Exposure	Participants	Combined *RR*	Men	Women	RR Adjusted for:
La Vecchia et al. (1993)	Italy	Acute MI	Spousal	113 AMI cases 225 hospital controls	1.2 (0.6, 2.5) Cigarette/day: <15: 1.1 >15: 1.3			Sex, age, education, coffee intake, body mass index, serum cholesterol, hypertension, diabetes, family history of MI
Layard (1995)	United States (National Mortality Follow-back Survey)	Fatal ischemic heart disease (ICD-9: 410–414)	Spousal	475 male IHD deaths/ 998 never smoking men; 914 female IHD deaths/ 1930 never smoking females		1.0 (0.7, 1.3) Cigarette/day: None: 1.0 1–14: 0.8 15–34: 1.1 35+: 0.9	1.0 (0.8, 1.2) Cigarettte/day: None: 1.0 1–14: 0.9 15–34: 1.2 35+: 1.1	Age, race
Lee et al. (1986)	United Kingdom	Ischemic heart disease	Spousal Score: (home, work, travel, leisure)	66 IHD cases, 254 controls	1.0 (0.7, 1.6) Score: 0–1: 1.0 2–4: 0.5 5–12: 0.6	1.2 (0.6, 2.8) Score: 0–1: 0.1 2–4: 0.4 5–12: 0.4	0.9 (0.6, 1.7) Score: 0–1: 1.0 2–4: 0.6 5–12: 0.8	
Muscat and Wynder (1995)	United States (New York, Philadelphia, Chicago, Detroit)	Myocardial infarction (ICD-9: 410.0)	Adult	68 male cases/ 108 never smoking male controls; 46 female cases/ 50 never smoking female controls		Years exposed: None: 1.0 1–20: 1.7 21–30: 1.5 >30: 1.1	Years exposed: None: 1.0 1–20: 2.0 21–30: 0.9 >30: 1.7	Age, education, hypertension
Palmer et al. 1988 (abstract)	United States (MA–unknown)	Myocardial infarction	Spousal (husband)	336 cases 799 hospital controls			1.2	Age
				Cross section				
Tunstall Pedoe et al. (1995)	Scotland	Nonfatal CHD	General	786 men 1492 never-smoking women	None: 1.0 Little: 1.2 Some: 1.5 A lot: 1.6			

also reported significantly increased risk for ischemic heart disease mortality for passive smokers. Similarly Garland and colleagues' study (1985) on a San Diego cohort demonstrated an increase in risk for death from ischemic heart disease from spousal ETS exposure (RR : 3.6 for former smokers, 2.7 for current smokers). While study details are not described in detail, Hunt Martin, and Williams (1986) found a risk estimate of 3.4 for incident fatal heart attacks in a Utah cohort of nonsmoking women married to smoking husbands.

Helsing and colleagues (1988) reported on heart disease mortality of nonsmokers enrolled in a cohort study in Washington County, Maryland. In comparison with persons married to nonsmokers, both men and women married to smokers had significantly increased risk of dying from heart disease (RR: 1.3 for males, 1.2 for females). In another report based on a cohort study in the United States, passive smoking was found to increase the risk of cardiovascular death (RR: 1.59; 95% CI: 0.99, 2.57) in nonsmoking participants in the Evans County, Georgia, cohort study (Humble et al., 1990).

Fatal and Nonfatal CHD Outcomes Several large cohort studies have been conducted that address both fatal and nonfatal CHD outcomes and ETS exposure. These studies include analyses of such large, national cohorts as the Nurses' Health Study, the American Cancer Society Cancer Prevention Study I and II (CPS-I and CPS-II), and the Multiple Risk Factor Intervention Trial (MRFIT). Except for the analyses of the CPS-I and CPS-II presented by LeVois and Layard (1995), all other studies demonstrated at least a modest increase in risk for fatal and nonfatal CHD due to ETS exposure.

Kawachi and colleagues' (1997) recent analysis of data from the Nurses' Health Study assessed both fatal CHD and nonfatal myocardial infarction due to exposure at home and work. Adjusting for a wide variety of CHD risk factors, any ETS exposure was associated with a risk of 1.71, occasional ETS exposure with a risk of 1.56 (95% CI: 0.9, 2.7), and regular ETS exposure with a risk of 1.97 (95% CI: 1.1, 3.3) for total CHD.

LeVois and Layard (1995), with support from the tobacco industry, analyzed data from the American Cancer Society's Cancer Prevention Study I and II (CPS-I and CPS-II). Males and females self-reported as never-smokers were not found to be more likely to die from CHD with increasing exposure to ETS. However, a significant increase in risk with passive exposure was reported for former smokers. Steenland and colleagues (1996) subsequently analyzed data from the same data set with the CPS-II cohort and conducted four different analyses on the data set. They found that nonsmoking men had a relative risk of 1.22 (95% CI: 1.07, 1.40) for ischemic heart disease (IHD) death when exposed to a current smoker. In fact, in all four analyses, significant positive associations were found for men currently exposed to ETS. Associations for women were nonsignificant.

The effect of involuntary smoking was also assessed among the nonsmoking male participants in the Multiple Risk Factor Intervention Trial (MRFIT); these men had been selected in 1973 to be in the upper 10% to 15% of risk for mortality for coronary artery disease, based on a score from the Framingham study (Svendsen et al., 1987). In comparison to men married to nonsmokers, never-smokers with smoking wives had increased risk for coronary heart disease (RR: 2.11; 95% CI: 0.69, 6.46); fatal or nonfatal coronary heart disease event (RR: 1.48; 95% CI: 0.89, 2.47), and death from any cause (RR: 1.96; 95% CI: 0.93, 4.11). These relative risks showed little change when former smokers were included in the analysis or when adjustments were made for other risk factors for coronary heart disease.

The unpublished dissertation of Butler (Grenier et al., 1992) on California Seventh Day Adventists also addressed nonfatal and fatal outcomes. This study assessed the risk of CHD due to spousal smoking, specifically on nonsmoking women married to husbands who smoked. Women exposed to husbands who were current smokers were found to have increased risk of CHD death (RR: 1.4; 95% CI: 0.5–3.8). Furthermore females working with smokers for 1 to 10 years and more than 11 years had relative risks of 1.85 and 1.86, respectively, compared with those working with nonsmokers.

Case-Control Studies

Fatal CHD Outcomes While the data from the cohort studies consistently demonstrated an increased risk for fatal CHD, the findings of case-control studies have been inconsistent. Layard (1995) conducted a case-control study on fatal ischemic heart disease among decedents from the 1986 National Mortality Followback Survey. In this study no increase in risk or dose-response of risk with exposure was observed for either never-smoking men or women who were married to spouses who did smoke. In contrast, Dobson and colleagues (1991) conducted a study in Australia and found an elevated risk of fatal myocardial infarction for nonsmoking women exposed to ETS at home (OR: 2.46; 95% CI: 1.47, 4.13), after adjusting for age and history of myocardial infarction.

Nonfatal CHD Outcomes A majority of the case-control studies investigated the association between ETS and nonfatal CHD outcomes. Ciruzzi and colleagues' recent (1996) case-control study in Argentina compared ETS exposure of acute myocardial infarction cases admitted into coronary care units to hospital controls. Persons exposed to one or more relatives who smoked had an odds ratio of 1.7 (95% CI: 1.2, 2.3) for acute myocardial infarction when compared to subjects exposed to relatives who did not smoke, after adjusting for a number of CHD risk factors. A similar hospital-based case-control study performed by La Vecchia and colleagues (1993) found an odds ratio of 1.2 for acute myocardial infarction in a cohort of men and women in Italy exposed to spouses who smoked, compared to never-smoking controls admitted to the same network of hospitals for acute diseases not related to cardiovascular risk factors. Risks were also demonstrated to be higher for persons with spouses smoking 15 or more cigarettes per day (RR: 1.3; 95% CI: 0.5, 3.4). Furthermore, in a hospital-based case-control study conducted in the United States, Muscat and Wynder (1995) observed an increased risk for myocardial infarction due to ETS exposure in both men and women. In this study, cases were defined as persons admitted to teaching hospitals in New York, Philadelphia, Chicago, and Detroit (OR: 1.5; 95% CI: 0.9, 2.6). However, a dose-response relationship was not observed. Palmer and colleagues (1989) also observed slightly higher risks for myocardial infarction in ETS-exposed women, although potential confounding risk factors were not accounted for.

Case-control studies have not shown an association between spousal smoking and either ischemic heart disease or stroke. For example, Lee, Chamberlain, and Alderson (1986) conducted a case-control study in England that failed to demonstrate an increased risk for ischemic heart disease or for stroke in nonsmokers married to smokers. However, the number of subjects in this study was small, and statistical power was accordingly limited.

The two studies conducted by He and colleagues in the People's Republic of China demonstrated elevated risks for nonfatal CHD. He and colleagues (1989) demonstrated an elevated risk for nonfatal CHD (OR: 3.0; 95% CI: 1.3, 7.2) for women married to husbands who were smokers, after adjusting for appropriate CHD risk factors. An increase in risk was also observed with the increasing number of cigarettes per day smoked by the husband. He and colleagues' second study in China (He et al., 1994) found that even though the risk for nonfatal CHD for women exposed to husbands and coworkers who smoked was not significantly increased, the risk did increase with the number of smokers to whom the women were exposed. The odds ratios for women whose husbands smoked was 1.24 (95% CI: 0.6, 2.7); however, like the initial 1989 study, this study had a modest sample size.

Fatal and Nonfatal CHD Outcomes Jackson, Proulx, and Pelican (1991) also assessed risk for both nonfatal CHD and fatal CHD in men and women. Risks were only elevated in women and only significant for fatal CHD (OR: 5.8; 95% CI: 1.3, 48.0). However, no adjustments were made for any risk factors associated with CHD.

Conclusions

There are strengths and weaknesses to both the case-control and cohort study designs in investigating ETS and CHD outcomes. Many of the case-control studies have small sample sizes and lack the power to detect significant associations. Furthermore many studies also lack information on other risk factors for CHD, and therefore they may not adequately adjust for confounders. In contrast, many of the cohort studies have large sample sizes and do adjust for confounders. They also avoid information bias by assessing smoking status and exposure prior to the CHD outcome. However, cohort studies are more susceptible to exposure misclassification due to the cessation or resumption of smoking by the source of exposure; this risk of misclassification increases with the length of follow-up.

Although the risk estimates for ETS and CHD outcomes vary, they range mostly from null to modestly significant increases in risk, with the risk for fatal outcomes generally higher and more significant. In their meta-analysis Law, Morris, and Wald (1997) estimated the excess risk from ETS exposure as 30% (95% CI: 22, 38%) at age 65 years. The California Environmental Protection Agency (Cal EPA, 1997) recently concluded that there is "an overall risk of 30%" for CHD due to exposure from ETS. The American Heart Association's Council on Cardiopulmonary and Critical Care has also concluded that environmental tobacco smoke both increases the risk of heart disease and is "a major preventable cause of cardiovascular disease and death" (Taylor, Johnson, and Kazemi, 1992). This conclusion was echoed in 1998 by the Scientific Committee on Tobacco and Health (Scientific Committee on Tobacco and Health and HSMO, 1998).

RESPIRATORY SYMPTOMS AND ILLNESSES IN ADULTS

Only a few cross-sectional investigations provide information on the association between respiratory symptoms in nonsmokers and involuntary exposure to tobacco smoke. These studies have primarily considered exposure outside the home. Consistent evidence of an effect of passive smoking on chronic respiratory symptoms in adults has not been found (Spengler and Ferris Jr., 1985; Lebowitz and Burrows, 1976; Schilling et al., 1977; Comstock et al., 1981; Schenker, Samet, and Speizer, 1982; Euler et al., 1987; Hole et al., 1989).

Two studies suggest that passive smoking may cause acute respiratory morbidity. Analysis of National Health Interview Survey data showed that a pack-a-day smoker increases respiratory restricted days by about 20% for a nonsmoking spouse (Ostro, 1989). In a study of determinants of daily respiratory symptoms in Los Angeles, student nurses with a smoking roommate significantly increased the risk of an episode of phlegm, after controlling for personal smoking (Schwartz and Zeger, 1990). Leuenberger and colleagues (1994) describe associations between passive exposure to tobacco smoke at home and in the workplace and respiratory symptoms in 4197 randomly selected never-smoking adults in the Swiss Study on Air Pollution and Lung Diseases in Adults, a multicenter study in eight areas of the country. Exposed subjects were those who reported any exposure during the past 12 months; exposed persons were then asked about workplace exposure and also the number of smokers and the duration of exposure at home and work together. Involuntary smoke exposure was associated with asthma, dyspnea, bronchitis and chronic bronchitis symptoms, and allergic rhinitis. The increments in risk were substantial, ranging from approximately 40% to 80% for the different respiratory outcome measures. The increments were not reduced by control for educational level; dose response relationships were found with the quantitative indicators of exposure. For several of the outcome measures, the dose response relationships tended to be steeper for those also reporting workplace exposure.

Other recent studies have also shown adverse effects of involuntary smoking on adults. Robbins, Abbey, and Lebowitz (1993) examined predictors of new symptoms compatible with "airway obstructive disease" in a cohort study of 3914 nonsmoking participants in the Adventist Health Study. Significantly increased risk was identified in association with exposure during both childhood and adulthood. In a cross-sectional study Dayal and colleagues (1994) found that never-smoking Philadelphia residents with a reported diagnosis of asthma, chronic bronchitis, or emphysema had sustained significantly greater exposure to tobacco smoke than unaffected controls.

Neither epidemiological nor experimental studies have established the role of ETS in exacerbating asthma in adults. The acute responses of asthmatics to ETS have been assessed by exposing persons with asthma to tobacco smoke in a chamber. This experimental approach cannot be readily controlled because of the impossibility of blinding subjects to exposure to ETS. However, suggestibility does not appear to underlie physiological responses of asthmatics of ETS (Urch et al., 1988). Of three studies involving exposure of unselected asthmatics to ETS, only one showed a definite adverse effect (Shephard, Collins, and Silverman, 1979; Dahms, Bolin, and Slavin, 1981; Murray and Morrison, 1986). Stankus et al. (1988) recruited 21 asthmatics who reported exacerbation with exposure to ETS. With challenge in an exposure chamber at concentrations much greater than typically encountered in indoor environments, 7 subjects experienced a more than 20% decline in FEV_1.

Lung Function in Adults

With regard to involuntary smoking and lung function in adults, exposure to passive smoking has been associated in cross-sectional investigations with reduction of the FEF_{25-75}. White and Froeb (1980) compared spirometric test results in middle-aged nonsmokers with at least 20 years of involuntary smoking in the workplace to the results in an unexposed control group of nonsmokers. The mean FEF_{25-75} of the exposed group was significantly reduced, by 15% of predicted value in women and by 13% in men. This investigation has been intensely criticized with regard to the spirometric test procedures, the determination and classification of exposures, and the handling of former smokers in the analyses.

A subsequently reported investigation in France examined the effect of marriage to a smoker in over 7800 adults in seven cities (Kauffmann, Tessier, and Oriol, 1983). The study included 849 male and 826 female nonsmokers exposed to tobacco smoking by their spouses' smoking. At age above 40 years, the FEF_{25-75} was reduced in nonsmoking men and women with a smoking spouse. The investigators interpreted this finding as representing a cumulative adverse effect of marriage to a smoker. In a subsequent report the original findings in the French women were confirmed, but a parallel analysis in a large population of U.S. women did not show effects of involuntary smoking on lung function (Spengler and Ferris Jr., 1985).

The results of an investigation of 163 nonsmoking women in the Netherlands also suggested adverse effects of tobacco smoke exposure in the home on lung function (Brunekreef et al., 1985; Remijn et al., 1985). Cross-sectional analysis of spirometric data collected in 1982 demonstrated adverse effects of tobacco smoke exposure in the home, but in a sample of the women, domestic exposure to tobacco smoke was not associated with longitudinal decline of lung function during the period 1965 to 1982.

Svendsen and coworkers (1987) assessed the effects of spouse smoking on 1400 nonsmoking male participants in the Multiple Risk Factor Intervention Trial (MRFIT). The subjects were aged 35 to 57 years at enrollment and were at high risk for mortality from coronary artery disease. At the baseline visit the maximum FEV_1 was approximately 3% lower for the men married to a smoker.

Masi and colleagues (1988) evaluated lung function of 293 young adults, using spirometry and measurement of the diffusing capacity and lung volumes. The results varied with gender. In men, reduction of the maximal midexpiratory flow rate was associated with maternal smoking and exposure to ETS during childhood. In women, reduction of the diffusing capacity was associated with exposure to ETS at work.

In the study of a general population sample in western Scotland, nonsmokers living with another household member who was a smoker had significantly reduced lung function in comparison with unexposed nonsmokers (Hole et al., 1989); the reduction of FEV_1 associated with involuntary smoking was about 5%. Passive smokers with higher exposure had greater reduction of the FEV_1.

Masjedi, Kazemi, and Johnson (1990) investigated the effects of passive smoking on lung function of 288 nonsmoking volunteers living in Tehran. Ventilatory function was reduced significantly for men exposed at work, although an additional effect of exposure at home was not found. Passive smoking at home and at work did not reduce the lung function of the female subjects.

Other studies have not shown chronic effects of involuntary exposure to tobacco smoke in adult nonsmokers. In two cross-sectional studies marriage to a smoker was not significantly associated with reduction of ventilatory function (Schilling et al., 1977; Comstock et al., 1981) Jones and coworkers (1983) conducted a case-control study of 20- to 39-year-old nonsmoking women in the longitudinal study in Tecumseh. Subjects from the highest and lowest quartiles of the lung-function distribution had comparable exposure to smokers in the home. In a study conducted in Germany, the effects of involuntary and active smoking were examined in a population of 1351 white-collar workers (Kentner, Triebig, and Weltle, 1984). Self-reported exposure to ETS at home and at work was not associated with reduction of spirometric measures of lung function. In a study of young Canadian adults, Jaakkola et al. (1995) did not find effects of home and workplace exposures on a change in lung function during an 8-year follow-up. In persons less than 26 years of age at enrollment, workplace ETS exposure was associated with greater decline.

Several investigators have reported associations of involuntary smoking with chronic obstructive pulmonary disease in nonsmokers. In the Japanese cohort study, a nonsignificant trend of increasing mortality from chronic bronchitis and emphysema with increasing passive exposure of nonsmoking women has been reported (Hirayama, 1984). Kalandidi and co-workers (1987) conducted a case-control study of involuntary smoking and chronic obstructive pulmonary disease; the cases were nonsmoking women with obstruction and reduction of the FEV_1 by at least 20%. Smoking by the husband was associated with a doubling of risk. Dayal et al. (1994) conducted a case-control study of self-reported obstructive lung disease in 219 never-smoking residents of Philadelphia. Household ETS exposure from one or more packs per day was associated with a doubling of risk. In a prospective cohort study of 3914 nonsmoking Adventists, ETS exposure was associated with report of symptoms considered to reflective of "airway obstructive disease" (Robbins, Abbey, and Lebowitz, 1993). An association of passive smoking with chronic obstructive pulmonary disease seems biologically implausible, however, since only a minority of active smokers develop this disease, and adverse effects of involuntary smoking on lung function in adults have not been observed consistently (DHHS, 1984). The autopsy study of Trichopoulus et al. (1992) does show, however, that airways of nonsmokers can be affected by ETS.

A conclusion cannot yet be reached on the effects of ETS exposure on lung function in adults. However, further research is warranted because of widespread exposure in workplaces and homes.

Odor and Irritation

Tobacco smoke contains numerous irritants, including particulate material and gases (DHHS, 1986b). Both questionnaire surveys and laboratory studies involving exposure to ETS have shown annoyance and irritation of the eyes and upper and lower airways from involuntary smoking. In several surveys of nonsmokers, complaints about tobacco smoke at work and in public places were common (DHHS, 1986b): About 50% of respondents complained about tobacco smoke at work, and a majority were disturbed by tobacco smoke in restaurants. The experimental studies show that the rate of eye blinking is increased by ETS, as are complaints of nose and throat irritation (DHHS, 1986b). In the study of passive smoking on commercial airline flights reported by Mattson and colleagues (1989), changes in nose and eye symptoms were associated with nicotine exposure. The odor and irritation associated with ETS merit special consideration because a high proportion of nonsmokers are annoyed by exposure to ETS, and control of concentrations in indoor air poses difficult problems in the management of heating, ventilating, and air-conditioning systems.

Using a challenge protocol, Bascom and colleagues (1991) showed that persons characterizing themselves as ETS-sensitive have greater responses on exposure than persons considering themselves as nonsensitive.

Other Effects

Other associations of passive smoking with adverse effects have been reported, most in relation to the fetus and children. A study of children with cystic fibrosis suggested that exposure to ETS at home adversely affects growth (Rubin, 1990).

This finding was not confirmed in a study of 340 patients with cystic fibrosis (Kovesi, Corey, and Levison, 1993). The investigators found that cessation of smoking was more likely in households of patients having lower lung function, indicating the potential for bias from differential patterns of smoking cessation.

In a study of 261 women aged 35 and over, passive smoking was found to alter the age at natural menopause (Everson et al., 1986). Passive exposure was associated with an approximately twofold increased risk of being menopausal.

Total Mortality

Several cohort studies provide information on involuntary smoking and mortality from all causes. In the Scottish cohort study, total mortality was initially reported as increased for women living with a smoker but not for men (Gillis et al., 1984). On further follow-up, all-cause mortality was increased in all passive smokers (RR: 1.27; 95% CI: 0.95, 1.70). As described previously, total mortality was also increased among nonsmoking participants in MRFIT who lived with smokers (Svendsen et al., 1987). In contrast, mortality was not increased for nonsmoking female subjects in a study in Amsterdam (Vandenbroucke et al., 1984). Neither the study in Scotland nor the study in Amsterdam controlled for other factors that influence total mortality. In the cohort study in Washington County, all-cause mortality rates were significantly increased for men (RR: 1.17) and for women (RR: 1.15) after adjustment for housing quality, schooling, and marital status (Sandler et al., 1989). All-cause mortality was also increased for passive smokers in the Evans County cohort (RR: 1.39; 95% CI: 0.99, 1.94).

Wells (1988) has made an estimate of the number of adult deaths in the United States attributable to passive smoking. The total is about 46,000, including 3000 from lung cancer, 11,000 from other cancers, and 32,000 from heart disease.

The small excesses of all-cause mortality associated with passive smoking in the epidemiological studies parallel the findings for cardiovascular disease, the leading cause of death in these cohorts. The increased risk of death associated with passive smoking has public health significance as an indicator of the overall impact of this avoidable exposure.

SUMMARY

The effects of active smoking and the toxicology of cigarette smoking have been comprehensively examined. The periodic reports of the U.S. Surgeon General and other summary reports have considered the extensive evidence on active smoking; these reports have provided definitive conclusions concerning the adverse effects of active smoking, which have prompted public policies and scientific research directed at prevention and cessation and smoking.

Although the evidence on involuntary smoking is not so extensive as that on active smoking, health risks of involuntary smoking have been identified and causal conclusions reached, beginning in the mid 1980s. The 1986 Report of the U.S. Surgeon General (DHHS, 1986b) and the 1986 Report of the National Research Council (NRC, 1986a) both concluded that involuntary exposure to tobacco smoke causes respiratory infections in children, increases the prevalence of respiratory symptoms in children, reduces the rate of functional growth as the lung matures, and causes lung cancer in nonsmokers. These conclusions have been reaffirmed in subsequent reports (EPA, 1992; Cal EPA, 1997; Ott, 1999) and new conclusions added. Involuntary smoking is now considered a cause of asthma, and a factor in exacerbating asthma (EPA, 1992; Cal EPA, 1997; Ott, 1999), and a cause of heart disease (Cal EPA, 1997; Ott, 1999). At the present time the evidence on passive smoking and cancer at sites other than the lung does not support causal conclusions.

The adverse effects of involuntary exposure to tobacco smoke have provided a strong rationale for policies directed at reducing and eliminating exposure of nonsmokers to ETS (DHHS, 1986b). Complete protection of nonsmokers in public locations and the workplace may require the banning of smoking, since the 1986 Report of the Surgeon General (DHHS, 1986b) concluded that "the simple separation of smokers and nonsmokers within the same air space may reduce, but does not eliminate, the exposure of nonsmokers to environmental tobacco smoke."

REFERENCES

Ahlborg, G., Jr., and L. Bodin. 1991. Tobacco smoke exposure and pregnancy outcome among working women: A prospective study at prenatal care centers in Orebro County, Sweden. *Am. J. Epidemiol.* 133(4): 338–347.

Allred, E. N., E. R. Bleecker, B. R. Chaitman, T. E. Dahms, S. O. Gottlieb, J. D. Hackney, M. Pagano, R. H. Selvester, S. M. Walden, and J. Warren. 1989. Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. *N. Engl. J. Med.* 321: 1426–1432.

Anderson, H. R., and D. G. Cook. 1997. Passive smoking and sudden infant death syndrome: Review of the epidemiological evidence. *Thorax* 52: 1003–1009.

Baghurst, P. A., S. L. Tong, A. Woodward, and A. J. McMichael. 1992. Effects of maternal smoking upon neuropsychological development in early childhood: Importance of taking account of social and environmental factors. *Paediatr. Perinat. Epidemiol.* 6: 403–415.

Barr, G. S., and A. P. Coatesworth. 1991. Passive smoking and otitis media with effusion. *Br. Med. J.* 303(6809): 1032–1033.

Bascom, R., T. Kulle, A. Kagey-Sobotka, and D. Proud. 1991. Upper respiratory tract environmental tobacco smoke sensitivity. *Am. Rev. Respir. Dis.* 143(6): 1304–1311.

Bauman, K. E., and R. L. Flewelling. 1991. Parental cigarette smoking and cognitive performance of children. *Health Psychol.* 10: 282–288.

Bauman, K. E., G. G. Koch, and L. A. Fisher. 1989. Family cigarette smoking and test performance by adolescents. *Health Psychol.* 8(1): 97–105.

Benowitz, N. L. 1996. Cotinine as a biomarker of environmental tobacco smoke exposure. *Epidemiol. Rev.* 18(2): 188–204.

Benowitz, N. L., F. Kuyt, P. Jacob, 3rd, R. T. Jones, and A. L. Osman. 1983. Cotinine disposition and effects. *Clin. Pharmacol. Ther.* 34: 604–611.

Bergman, A. B., and L. A. Wiesner. 1976. Relationship of passive cigarette-smoking to sudden infant death syndrome. *Pediatrics* 58(5): 665–668.

Berkey, C. S., J. H. Ware, and D. W. Dockery. 1986. Indoor air pollution and pulmonary function growth in preadolescent children. *Am. J. Epidemiol.* 123: 250–260.

Black, N. 1985. The aetiology of glue ear — A case-control study. *Int. J. Pediatr. Otorhinolaryngol.* 9: 121–133.

Blair, P. S., P. J. Fleming, D. Bensley, I. Smith, C. Bacon, E. Taylor, J. Berry, J. Golding, and J. Tripp. 1996. Smoking and the sudden infant death syndrome: Results from 1993–1995 case-control study for confidential inquiry into stillbirths and deaths in infancy. *Br. Med. J.* 313: 195–198.

Brownson, R. C., M. C. Alavanja, E. T. Hock, and T. S. Loy. 1992. Passive smoking and lung cancer in nonsmoking women. *Am. J. Public Health* 82(11): 1525–1530.

Brunekreef, B., P. Fischer, B. Remijn, R. Van Der Lende, J. Schouten, and P. Quanjer. 1985. Indoor air pollution and its effect on pulmonary function of adult nonsmoking women. III. Passive smoking and pulmonary function. *Int. J. Epidemiol.* 14: 227–230.

Buckley, J. D., W. L. Hobbie, K. Ruccione, H. N. Sather, W. G. Wood, and G. D. Hammond. 1986. Maternal smoking during pregnancy and the risk of childhood cancer. *Lancet* 1: 519–520.

Burchfiel, C. M., III. 1984. *Passive smoking, respiratory symptoms, lung function and initiation of smoking in Tecumseh, Michigan.* PhD dissertation. University of Michigan, Ann Arbor.

Burchfiel, C. M., M. W. Higgins, J. B. Keller, W. F. Howatt, W. J. Butler, and I. T. T. Higgins. 1986. Passive smoking in childhood: Respiratory conditions and pulmonary function in Tecumseh, Michigan. *Am. Rev. Respir. Dis.* 133: 966–973.

Cal EPA. 1996. *Evidence on Developmental and Reproductive Toxicity of Cadmium: Reproductive and Cancer Hazard Assessment Section.* Sacramento, California Environmental Protection Agency.

Cal EPA. 1997. *Health Effects of Exposure to Environmental Tobacco Smoke.* California Environmental Protection Agency.

Cardenas, V. M., M. J. Thun, H. Austin, C. A. Lally, W. S. Clark, R. S. Greenberg, and C. W. J. Heath. 1997. Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's Cancer Prevention Study. II. *Cancer Causes Control* 8(1): 57–64.

Charlton, A. 1984. Children's coughs related to parental smoking. *Br. Med. J.* 288: 1647–1649.

Ciruzzi, M., O. Estaban, J. Roziosnik, H. Montagna, J. Caccavo, D. De La Cruz, D. Ojoda, J. Piskorz, J. De Ross, P. Pramparo, and H. Schargrodsky. 1996. Passive smoking and the risk of acute myocardial infarction. XVIIIth Congress of the European Society of Cardiology. *Eur. Heart J.* 309(suppl).

Claxton, L. D., R. S. Morin, T. J. Hughes, and J. Lewtas. 1989. A genotoxic assessment of environmental tobacco smoke using bacterial bioassays. *Mutat. Res.* 222(2): 81–99.

Coghlin, J., S. K. Hammond, and P. H. Gann. 1989. Development of epidemiologic tools for measuring environmental tobacco smoke exposure. *Am. J. Epidemiol.* 130(4): 696–704.

Collet, J. P., C. P. Larson, J. F. Boivin, S. Suissa, and B. Pless. 1995. Parental smoking and risk of otitis media in pre-school children. *Can. J. Public Health* 86: 269–273.

Colley, J. R. T., W. W. Holland, and R. T. Corkhill. 1974. Influence of passive smoking and parental phlegm on pneumonia and bronchitis in early childhood. *Lancet* 2: 1031–1034.

Comstock, G. W., and F. E. Lundin. 1967. Parental smoking and perinatal mortality. *Am. J. Obstet. Gynecol.* 98(5): 708–718.

Comstock, G. W., M. B. Meyer, K. J. Helsing, and M. S. Tockman. 1981. Respiratory effects of household exposures to tobacco smoke and gas cooking. *Am. Rev. Respir. Dis.* 124: 143–148.

Cook, D. G., and D. P. Strachan. 1997. Parental smoking and prevalence of respiratory symptoms and asthma in school age children. *Thorax* 52(12): 1081–1094.

Coultas, D. B., C. A. Howard, G. T. Peake, B. J. Skipper, and J. M. Samet. 1987. Salivary cotinine levels and involuntary tobacco smoke exposure in children and adults in New Mexico. *Am. Rev. Respir. Dis.* 136(2): 305–309.

Coultas, D. B., G. T. Peake, and J. M. Samet. 1989. Questionnaire assessment of lifetime and recent exposure to environmental tobacco smoke. *Am. J. Epidemiol.* 130: 338–347.

Coultas, D. B., J. M. Samet, J. F. McCarthy, and J. D. Spengler. 1990a. Variability of measures of exposure to environmental tobacco smoke in the home. *Am. Rev. Respir. Dis.* 142: 602–606.

Coultas, D. B., J. M. Samet, J. F. McCarthy, and J. D. Spengler. 1990b. A personal monitoring study to assess workplace exposure to environmental tobacco smoke. *Am. J. Public Health* 80(8): 988–990.

Crawford, F. G., J. Mayer, R. M. Santella, T. B. Cooper, R. Ottman, W. Y. Tsai, G. Simon-Cereijido, M. Wang, D. Tang, and F. P. Perera. 1994. Biomarkers of environmental tobacco smoke in preschool children and their mothers. *J. Natl. Cancer Inst.* 86(18): 1398–1402.

Cummings, K. M., S. J. Marbello, M. C. Mahoney, and J. R. Marshall. 1989. Measurement of lifetime exposure to passive smoke. *Am. J. Epidemiol.* 130: 122–132.

Cummings, K. M., S. J. Markello, M. Mahoney, A. K. Bhargava, P. D. McElroy, and J. R. Marshall. 1990. Measurement of current exposure to environmental tobacco smoke. *Arch. Environ. Health* 45(2): 74–79.

Dahms, T. E., J. F. Bolin, and R. G. Slavin. 1981. Passive smoking: Effect on bronchial asthma. *Chest* 80(5): 530–534.

Dayal, H. H., S. Khuder, R. Sharrar, and N. Trieff. 1994. Passive smoking in obstructive respiratory disease in an industrialized urban population. *Environ. Res.* 65(2): 161–171.

Denson, R., J. L. Nanson, and M. A. McWatters. 1975. Hyperkinesis and maternal smoking. *Can. Psychiatr. Assoc.* 20: 183–187.

DHEW. 1979. *Changes in Cigarette Smoking and Current Smoking Practices Among Adults: United States, 1978.* Washington, DC : U.S. Government Printing Office, Advance Data 52.

DHHS. 1980. *The Health Consequences of Smoking for Women: A Report of the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office of Smoking and Health.

DHHS. 1982. *The Health Consequences of Smoking: Cancer. A Report of the Surgeon General.* Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, DHHS Publication (PHS) 82-50179.

DHHS. 1984. *The Health Consequences of Smoking — Chronic Obstructive Lung Disease. A report of the Surgeon General.* Washington, DC: U.S. Government Printing Office.

DHHS. 1986a. *Smoking and Health: A National Status Report to Congress.* Rockville, MD: U.S. Government Printing Office.

DHHS. 1986b. *The Health Consequences of Involuntary Smoking. A Report of the Surgeon General.* Washington, DC: U.S. Government Printing Office, DHHS Publication (CDC) 87-8398.

DHHS. 1988. *The Health Consequences of Smoking: Nicotine Addiction. A report of the Surgeon General.* Washington, DC: U.S. Government Printing Office.

DHHS. 1989. *Reducing the Health Consequences of Smoking: 25 years of progress. A report of the Surgeon General.* Washington, DC: U.S. Government Printing Office.

DHHS. 1990a. Current estimates from the National Health Interview Survey, 1990. Series 10: Data from the National Health Interview Survey. *Department of Health and Human Services* 181. DHHS Publication (PHS) 91-1509.

DHHS. 1990b. *Smoking, Tobacco, and Cancer Program, 1985–1989 Status Report.* Washington, DC: U.S. Government Printing Office, NIH Publication No. 90-3107.

DHHS. 1990c. *The Health Benefits of Smoking Cessation. A report of the Surgeon General.* Washington, DC: U.S. Government Printing Office.

DHHS, Public Health Service, Centers for Disease Control and Prevention (CDC), National Center for Chronic Disease Prevention and Health Promotion, and Office on Smoking and Health. 1994. *Preventing Tobacco Use among Young People: A Report of the Surgeon General.* Washington, DC: U.S. Government Printing Office.

DHHS. 1997. *Practical Guide for the Diagnosis and Management of Asthma.* NIH Report 97-4053.

Dobson, A. J., H. M. Alexander, R. F. Heller, and D. M. Lloyd. 1991. Passive smoking and the risk of heart attack or coronary death. *Med. J. Aust.* 154: 793–797.

Enstrom, J. E. 1979. Rising lung cancer mortality among nonsmokers. *J. Natl. Cancer Inst.* 62: 755–760.

EPA. 1992. *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders.* Washington, DC: U.S. Government Printing Office, EPA/600/006F.

Eskenazi, B., and J. J. Bergmann. 1995. Passive and active maternal smoking during pregnancy as measured by serum cotinine, and postnatal smoke exposure. I. Effects on physical growth at age 5 years. *Am. J. Public Health* 142: S10–S18.

Eskenazi, B., and L. S. Trupin. 1995. Passive and active maternal smoking during pregnancy, as measured by serum cotinine, and postnatal smoke exposure. II. Effects on neurodevelopment at age 5 years. *Am. J. Public Health* 142: S19–S29.

Etzel, R. A., E. N. Pattishall, N. Haley, R. H. Fletcher, and F. W. Henderson. 1992. Passive smoking and middle ear effusion among children in day care. *Pediatrics* 90: 228–232.

Euler, G. L., D. E. Abbey, A. R. Magie, and J. E. Hodgkin. 1987. Chronic obstructive pulmonary disease symptom effects of long-term cumulative exposure to ambient levels of total suspended particulates and sulfur dioxide in California Seventh-Day Adventist residents. *Arch. Environ. Health.* 42(4): 213–222.

Evans, D., M. J. Levison, C. H. Feldman, N. M. Clark, Y. Wasilewski, B. Levin, and R. B. Mellins. 1987. The impact of passive smoking on emergency room visits of urban children with asthma. *Am. Rev. Respir. Dis.* 135: 567–572.

Everson, R. B., D. P. Sandler, A. J. Wilcox, D. Schreinemachers, D. L. Shore, and C. Weinberg. 1986. Effect of passive exposure to smoking on age at natural menopause. *Br. Med. J. (Clin. Res. Ed.)* 293: 792.

Ey, J. L., C. J. Holberg, M. B. Aldous, A. L. Wright, F. D. Martinez, and L. M. Taussig. 1995. Passive smoke exposure and otitis media in the first year of life. Group Health Medical Associates. *Pediatrics* 95(5): 670–677.

First, M. W. 1985. Constituents of sidestream and mainstream tobacco and markers to quantify exposure to them. In *Indoor air and human health,* ed. R. B. Gammage. Chelsea. MI: Lewis Publishers.

Fleming, D. W., S. L. Cochi, A. W. Hightower, and C. V. Broome. 1987. Childhood upper respiratory tract infections: To what degree is incidence affected by day-care attendance? *Pediatrics* 79(1): 55 – 60.

Foliart, D., N. L. Benowitz, and C. E. Becker. 1983. Passive absorption of nicotine in flight attendants. *N. Engl. J. Med.* 308: 1105.

Fontham, E. T. H., P. Correa, P. Reynolds, A. Wu-Williams, P. A. Buffler, R. S. Greenberg, V. W. Chen, T. Alterman, P. Boyd, D. F. Austin, and J. Liff. 1994. Environmental tobacco smoke and lung cancer in nonsmoking women: A multicenter study. *JAMA* 271(22): 1752–1759.

Friedman, G. D., D. B. Petitti, and R. D. Bawol. 1983. Prevalence and correlates of passive smoking. *Am. J. Public Health* 73: 401 – 405.

Garfinkel, L. 1981. Time trends in lung cancer mortality among nonsmokers and a note on passive smokers. *J. Natl. Cancer Inst.* 66(6): 1061–1066.

Garland, C., E. Barret-Connor, L. Suarez, M. H. Criqui, and D. L. Wingard. 1985. Effects of passive smoking on ischemic heart disease mortality of nonsmokers: A prospective study. *Am. J. Epidemiol.* 121(5): 645–650.

Gillis, C. R., D. J. Hole, V. M. Hawthorne, and P. Boyle. 1984. The effect of environmental tobacco smoke in two urban communities in the west of Scotland. *Eur. J. Respir. Dis.* 65: 121–126.

Glantz, S. A., and W. W. Parmley. 1991. Passive smoking and heart disease: Epidemiology, physiology, and biochemistry. *Circulation* 83: 1–12.

Glantz, S. A., and W. W. Parmley. 1995. Passive smoking and heart disease: Mechanisms and risk. *JAMA* 273(13): 1047–1053.

Green, R. E., and N. K. Cooper. 1991. Passive smoking and middle ear effusions in children in British servicemen in West Germany—A point prevalence survey by clinics of outpatient attendance. *J. Army Med. Corps* 137(1): 31–33.

Greenberg, R. A., N. J. Haley, R. A. Etzel, and F. A. Loda. 1984. Measuring the exposure of infants to tobacco smoke: Nicotine and cotinine in urine and saliva. *N. Engl. J. Med.* 310: 1075–1078.

Grenier, M. G., S. G. Hardcastle, G. Kunchur, and K. Butler. 1992. The use of tracer gases to determine dust dispersion patterns and ventilation parameters in a mineral processing plant. *Am. Ind. Hyg. Assoc. J.* 53: 387–394.

Grufferman, S., H. H. Wang, E. R. DeLong, S. Y. Kimm, E. S. Delzell, and J. M. Falletta. 1982. Environmental factors in the etiology of rhabdomyosarcoma in childhood. *J. Natl. Cancer Inst.* 68(1): 107–113.

Guerin, M. R., R. A. Jenkins, and B. A. Tomkins. 1992. *The Chemistry of Environmental Tobacco Smoke: Composition and Measurement*. Chelsea, MI: Lewis Publishers.

Hackshaw, A. K., M. R. Law, and N. J. Wald. 1997. The accumulated evidence on lung cancer and environmental tobacco smoke. *Br. Med. J.* 315(7114): 980–988.

Haddow, J. E., G. J. Knight, G. E. Palomaki, and J. E. McCarthy. 1988. Second-trimester serum cotinine levels in nonsmokers in relation to birth weight. *Am. J. Obstet. Gynecol.* 159(2): 481–484.

Haley, N. J., S. G. Colosimo, C. M. Axelrod, R. Hanis, and D. W. Sepkovic. 1989. Biochemical validation of self-reported exposure to environmental tobacco smoke. *Environ. Res.* 49: 127–135.

Hammond, S. K. 1999. Exposure of U.S. Workers to Environmental Tobacco Smoke. *Environ. Health. Perspect.* 107(suppl 2): 329–340.

Hammond, S. K., and B. P. Leaderer. 1987. A diffusion monitor to measure exposure to passive smoking. *Environ. Sci. Technol.* 21: 494–497.

Hanrahan, J. P., I. B. Tager, M. R. Segal, T. D. Tosteson, R. G. Castile, H. Van Vunakis, S. T. Weiss, and F. E. Speizer. 1992. The effect of maternal smoking during pregnancy on early infant lung function. *Am. Rev. Respir. Dis.* 145:1129–1135.

Harlap, S., and A. M. Davies. 1974. Infant admissions to hospital and maternal smoking. *Lancet* 1: 529–532.

Harlos, D. P., M. Marbury, J. M. Samet, and J. D. Spengler. 1987. Relating indoor NO_2 levels to infant personal exposures. *Atmos. Environ.* 21: 369–378.

Harper, R. M., and R. C. Frysinger. 1988. Suprapontine mechanisms underlying cardiorespiratory regulation: Implications for the sudden infant syndrome. In *Sudden Infant Death Syndrome: Risk Factors and Basic Mechanism*, eds. R. M. Harper and J. H. Hoffman. New York: SP Medical and Scientific Books, pp. 399–412.

Hartley, A. L., J. M. Birch, P. A. McKinney, M. D. Teare, V. Blair, J. Carrette, J. R. Mann, G. J. Draper, C. A. Stiller, and H. E. Johnston. 1988. The Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC): Case control study of children with bone and soft tissue sarcomas. *Br. J. Cancer* 58(6): 838–842.

He, Y., L. S. Li, Z. H. Wan, X. L. Zheng, and G. L. Jia. 1989. Women's passive smoking and coronary heart disease. *Chin. J. Prev. Med.* 23(1): 19–22.

He, Y., T. H. Lam, L. S. Li, R. Y. Du, G. L. Jia, J. Y. Huang, and J. S. Zheng. 1994. Passive smoking at work as a risk factor for coronary heart disease in Chinese women who have never smoked. *Br. Med. J.* 308: 380–384.

Hecht, S. S., S. G. Carmella, S. E. Murphy, S. Akerkar, K. D. Brunnemann, and D. Hoffmann. 1993. A tobacco-specific lung carcinogen in the urine of men exposed to cigarette smoke. *N. Engl. J. Med.* 93(21): 1543–1546.

Helsing, K. J., D. P. Sandler, G. W. Comstock, and E. Chee. 1988. Heart disease mortality in nonsmokers living with smokers. *Am. J. Epidemiol.* 127(5): 915–922.

Henderson, F. W., H. F. Reid, R. Morris, O. L. Wang, P. C. Hu, R. W. Helms, L. Forehand, J. Mumford, J. Lewtas, N. J. Haley, and S. K. Hammond. 1989. Home air nicotine levels and urinary cotinine excretion in preschool children. *Am. Rev. Respir. Dis.* 140: 197–201.

Hinton, A. E., and G. Buckley. 1988. Parental smoking and middle ear effusions in children. *J. Laryngol. Otol.* 102(11): 992–996

Hirayama, T. 1981. Non-smoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan. *Br. Med. J. (Clin. Res. Ed.)* 282(6259): 183–185.

Hirayama, T. 1984. Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. *Prev. Med.* 13: 680–690.

Hoffman, D., N. J. Haley, J. D. Adams, and K. D. Brunnemann. 1984. Tobacco sidestream smoke: Uptake by nonsmokers. *Prev. Med.* 13: 608–617.

Hole, D. J., C. R. Gillis, C. Chopra, and V. M. Hawthorne. 1989. Passive smoking and cardiorespiratory health in a general population in the west of Scotland. *Br. Med. J.* 299(6696): 423–427.

Hosein, H. R., C. A. Mitchell, and A. Bouhuys. 1977. Evaluation of outdoor air quality in rural and urban communities. *Arch. Environ. Health* 32(1): 4–13.

Hosein, R., and P. Corey. 1984. Multivariate analyses of nine indoor factors on FEV_1 of Caucasian children. *Am. Rev. Respir. Dis.* 129: A140

Howe, G. R., J. D. Burch, A. M. Chiarelli, H. A. Risch, and B. C. Choi. 1989. An exploratory case-control study of brain tumors in children. *Cancer Res.* 49: 4349–4352.

Huel, G., J. Godin, T. Moreau, F. Girard, J. Sahuquillo, G. Hellier, and P. Blot. 1989. Aryl hydrocarbon hydroxylase activity in human placenta of passive smokers. *Environ. Res.* 50(1): 173–183.

Humble, C., J. Croft, A. Gerber, M. Casper, C. G. Hames, and H. A. Tyroler. 1990. Passive smoking and 20-year cardiovascular disease mortality among nonsmoking wives, Evans County, Georgia. *Am. J. Public Health* 80(5): 599–601.

Hunt, S. C., M. J. Martin, and R. R. Williams. 1986. Passive smoking by nonsmoking wives is associated with an increased incidence of heart disease in Utah, 86 A.D., at Las Vegas, NV: Am Public Hlth Assoc Mtg.

Husgafvel-Pursiainen, K., M. Sorsa, K. Engstrom, and P. Einisto. 1987. Passive smoking at work: Biochemical and biological measures of exposure to environmental tobacco smoke. *Int. Arch. Occup. Environ. Health.* 59(4):337–345.

IARC. 1986. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Smoking*. Lyon, France: International Agency for Research on Cancer, World Health Organization, IARC.

Idle, J. R. 1990. Titrating exposure to tobacco smoke using cotinine — A minefield of misunderstandings. *J. Clin. Epidemiol* 43(4): 313–317.

Iversen, M., L. Birch, G. R. Lundqvist, and O. Elbrond. 1985. Middle ear effusion in children and the indoor environment: An epidemiological study. *Arch. Environ. Health* 40: 74–79.

Jaakkola, M. S., and J. J. K. Jaakkola. 1997. Assessment of exposure to environmental tobacco smoke. *Eur. Respir. J.* 10: 2384–2397.

Jaakkola, M. S., J. J. K. Jaakkola, M. R. Becklake, and P. Ernst. 1995. Passive smoking and evolution of lung function in young adults: An eight-year longitudinal study. *J. Clin. Epidemiol.* 48: 317–327.

Jackson, M. Y., J. M. Proulx, and S. Pelican. 1991. Obesity prevention. *Am. J. Clin. Nutr.* 91(6 suppl): 1625S–1630S.

Jarvis, M. J., and M. A. Russell. 1984. Measurement and estimation of smoke dosage to non-smokers from environmental tobacco smoke. *Eur. J. Respir. Dis.* 133 (suppl): 68–75.

Jarvis, M. J., M. A. H. Russell, N. L. Benowitz, and C. Feyerabend. 1988. Elimination of cotinine from body fluids: Implications for noninvasive measurement of tobacco smoke exposure. *Am. J. Public Health* 78: 696–698.

Jarvis, M. J., M. A. Russell, C. Feyerabend, J. R. Eiser, M. Morgan, P. Gammage, and E. M. Gray. 1985. Passive exposure to tobacco smoke: saliva cotinine concentrations in a representative population sample of nonsmoking school children. *Br. Med. J.* 291: 927–929.

Jenkins, M. A., J. R. Clarke, J. B. Carlin, C. F. Robertson, J. L. Hopper, M. F. Dalton, D. P. Holst, K. Choi, and G. G. Giles. 1996. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int. J. Epidemiol.* 25(3): 609–616.

John, E. M., D. A. Savitz, and D. P. Sandler. 1991. Prenatal exposure to parents' smoking and childhood cancer. *Am. J. Epidemiol.* 133(2): 123–132.

Jones, J. R., I. T. T. Higgins, M. W. Higgins, and J. B. Keller. 1983. Effects of cooking fuels on lung function in nonsmoking women. *Arch. Environ. Health.* 38: 219–222.

Kabat, G. C., G. S. Dieck, and E. L. Wynder. 1986. Bladder cancer in nonsmokers. *Cancer* 2: 362–367.

Kabat, G. C., S. D. Stellman, and E. L. Wynder. 1995. Relation between exposure to environmental tobacco smoke and lung cancer in lifetime nonsmokers. *Am. J. Epidemiol.* 142(2): 141–148.

Kalandidi, A., D. Trichopoulos, A. Hatzakis, S. Tzannes, and R. Saracci. 1987. Passive smoking and chronic obstructive lung disease. *Lancet* 2(8571): 1325–1326.

Kallail, K. J., H. R. Rainbolt, and M. D. Bruntzel. 1987. Passive smoking and middle ear problems in Kansas public school children. *J. Commun. Disord.* 20(3): 187–196.

Kauffmann, F., J. S. Tessier, and P. Oriol. 1983. Adult passive smoking in the home environment: A risk factor for chronic airflow limitation. *Am. J. Epidemiol.* 117: 269–280.

Kawachi, I., G. A. Colditz, F. E. Speizer, J. E. Manson, M. J. Stampfer, W. C. Willett, and C. H. Hennekens. 1997. A prospective study of passive smoking and coronary heart disease. *Circulation* 95(10): 2374–2379.

Kentner, M., G. Triebig, and D. Weltle. 1984. The influence of passive smoking on pulmonary function — A study of 1,351 office workers. *Prev. Med.* 13: 656–669.

Kitchens, G. G. 1995. Relationship of environmental tobacco smoke to otitis media in young children. *Laryngoscope* 105: 1–12.

Klonoff-Cohen, H. S., S. L. Edelstein, E. S. Lefkowitz, I. P. Srinivasan, D. Kaegi, J. C. Chang, and K. J. Wiley. 1995. The effect of passive smoking and tobacco exposure through breast milk on sudden infant death syndrome. *JAMA* 273(10): 795–798.

Kovesi, T., M. Corey, and H. Levison. 1993. Passive smoking and lung function in cystic fibrosis. *Am. Rev. Respir. Dis.* 148(5): 1266–1271.

Kraemer, M. J., M. A. Richardson, N. S. Weiss, C. T. Furukawa, G. G. Shapiro, W. E. Pierson, and C. W. Bierman. 1983. Risk factors for persistent middle-ear effusions: Otitis media, catarrh, cigarette smoke exposure, and atopy. *JAMA* 83(8): 1022–1025.

Kramer, S., E. Ward, A. T. Meadows, and K. E. Malojne. 1987. Medical and drug risk factors associated with neuroblastom: A case control study. *J. Natl. Cancer Inst.* 78(5): 797–804.

Kyerematen, G. A., M. D. Damiano, B. H. Dvorchik, and E. S. Vesell. 1982. Smoking-induced changes in nicotine disposition: Application of a new HPLC assay for nicotine and its metabolites. *Clin. Pharmacol. Ther.* 32: 769–780.

La Vecchia, C., B. D'Avanzo, M. G. Franzosi, and G. Tognoni. 1993. Passive smoking and the risk of acute myocardial infarction. *Lancet* 341: 505–506.

Law, M. R., and A. K. Hackshaw. 1997. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: Recognition of a major effect. *Br. Med. J.* 315(7112): 841–846.

Law, M. R., J. K. Morris, and N. J. Wald. 1997. Environmental tobacco smoke exposure and ischaemic heart disease: An evaluation of the evidence. *Br. Med. J.* 315(7114): 973–980.

Layard, M. W. 1995. Ischemic heart disease and spousal smoking in the National Mortality Followback Survey. *Regul. Toxicol. Pharmacol.* 21: 180–183.

Leaderer, B. P., and S. K. Hammond. 1991. Evaluation of vapor-phase nicotine and respirable suspended particle mass as markers for environmental tobacco smoke. *Environ. Sci. Technol.* 25: 770–777.

Lebowitz, M. D. 1984. The effects of environmental tobacco smoke exposure and gas stoves on daily peak flow rates in asthmatic and non-asthmatic families. *Eur. J. Respir. Dis.* 133: 90–97.

Lebowitz, M. D., and B. Burrows. 1976. Respiratory symptoms related to smoking habits of family adults. *Chest* 69: 48–50.

Lebowitz, M. D., and C. J. Holberg. 1988. Effects of parental smoking and other risk factors on the development of pulmonary function in children and adolescents. *Am. J. Epidemiol.* 128: 589–597.

Lee, P. N. 1988. *Misclassification of Smoking Habits and Passive Smoking*. Berlin: Springer Verlag.

Lee, P. N., J. Chamberlain, and M. R. Alderson. 1986. Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. *Br. J. Cancer* 54(1): 97–105.

Leuenberger, P., J. Schwartz, U. Ackermann-Liebrich, K. Blaser, G. Bolognini, J. P. Bongard, O. Brandli, P. Braun, C. Bron, M. Brutsche, et al. 1994. Passive smoking exposure in adults with chronic respiratory symptoms (SAPALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. *Am. J. Resp. Crit. Care. Med.* 150(5 Pt 1): 1222–1228.

LeVois, M. E., and M. W. Layard. 1995. Publication bias in the environmental tobacco smoke/coronary heart disease epidemiologic literature. *Regul. Toxicol. Pharmacol.* 21: 184–191.

Lindbohm, M. L., M. Sallmen, K. Hemminki, and H. Taskinen. 1991. Paternal occupational lead exposure and spontaneous abortion. *Scand. J. Work. Environ. Health* 17: 95–103.

Lofroth, G. 1989. Environmental tobacco smoke: Overview of chemical composition and genotoxic components. *Mutat. Res.* 222(2): 73–80.

Maclure, M., R. B. Katz, M. S. Bryant, P. L. Skipper, and S. R. Tannenbaum. 1989. Elevated blood levels of carcinogens in passive smokers. *Am. J. Public Health* 89(10): 1381–1384.

Magnani, C., G. Pastore, L. Luzzatto, and B. Terracini. 1990. Parent at occupation and other environmental factors in the etiology of leukemia's and non-Hodgkins lymphomas in childhood: A case-control study. *Stumori* 76: 413–419.

Mainous, A. G., and W. J. Hueston. 1994. Passive smoke and low birth weight: Evidence of a threshold effect. *Arch. Fam. Med.* 3: 875–878.

Makin, J., P. A. Fried, and B. Watkinson. 1991. A comparison of active and passive smoking during pregnancy: Long-term effects. *Neurotoxicol. Teratol.* 13(1): 5–12.

Martin, T. R., and M. B. Bracken. 1986. Association of low birth weight with passive smoke exposure in pregnancy. *Am. J. Epidemiol.* 124(4): 633–642.

Martinez, F. D., A. L. Wright, L. M. Taussig, and Group Health Medical Associates. 1994. The effect of paternal smoking on the birthweight newborns whose mothers did not smoke. *Am. J. Public Health* 84(9): 1489–1491.

Martinez, F. D., G. Antognoni, F. Macri, E. Bonci, F. Midulla, G. DeCastro, and R. Ronchetti. 1988. Parental smoking enhances bronchial responsiveness in nine-year-old children. *Am. Rev. Respir. Dis.* 138: 518–523.

Masi, M. A., J. A. Hanley, P. Ernst, and M. R. Becklake. 1988. Environmental exposure to tobacco smoke and lung function in young adults. *Am. Rev. Respir. Dis.* 138: 296–299.

Masjedi, M. R., H. Kazemi, and D. C. Johnson. 1990. Effects of passive smoking on the pulmonary function of adults. *Thorax* 45(1): 27–31.

Matanoski, G., S. Kanchanaraksa, D. Lantry, and Y. Chang. 1995. Characteristics of nonsmoking women in NHANES I and NHANES I epidemiologic follow-up study with exposure to spouses who smoke. *Am. J. Epidemiol.* 142(2): 149–157.

Mattson, M. E., G. Boyd, D. Byor, C. Brown, J. F. Callahan, D. Corle, J. W. Cullen, J. Greenblatt, N. J. Haley, K. Hammond, J. Lewtas, and W. Reeves. 1989. Passive smoking on commercial airline flights. *JAMA* 261: 867–872.

Mau, G., and P. Netter. 1974. The effects of paternal cigarette smoking on perinatal mortality and the incidence of malformations. *Dtsch. Med. Wochenschr.* 99(21): 1113–1118.

McCredie, M., P. Maisonneuve, and P. Boyle. 1994. Antenatal risk factors for malignant brain tumors in New South Wales children. *Int. J. Cancer* 56: 6–10.

McGlashan, N. D. 1989. Sudden infant deaths in Tasmania, 1980-1986: A seven-year prospective study. *Soc. Sci. Med.* 29: 1015–1026.

McKinney, P. A., R. A. Cartwright, J. M. Saiu, J. R. Mann, C. A. Stiller, G. J. Draper, A. L. Hartley, P. A. Hopton, J. M. Birch, and J. A. Waterhouse. 1987. The inter-regional epidemiological study of childhood cancer (IRESCC): A case control study of aetiological factors in leukaemia and lymphoma. Arch. Dis. Child. 62(3): 279–287. (Published erratum appears in *Arch. Dis. Child* 1987 Jun; 62(6): 644).

McLaughlin, J. K., M. S. Dietz, E. S. Mehl, and W. J. Blot. 1987. Reliability of surrogate information on cigarette smoking by type of informant. *Am. J. Epidemiol.* 126(1): 144–146.

Milerad, J., and H. Sundell. 1993. Nicotine exposure and the risk of SIDS. *Acta Paediatr. Scand.* 389(suppl): 70–72.

Miller, G. H. 1984. Cancer, passive smoking and nonemployed and employed wives. *West. J. Med.* 140: 632–635.

Mitchell, E. A., L. Scragg, and M. Clements. 1995. Location of smoking and the sudden infant death syndrome (SIDS). *Aust. N. Z. J. Med.* 25: 155–156.

Mitchell, E. A., R. P. K. Ford, A. W. Stewart, B. J. Taylor, D. M. O. Becroft, J. M. D. Thompson, R. Scragg, I. B. Hassall, D. M. J. Barry, E. M. Allen, and A. P. Roberts. 1993. Smoking and the sudden infant death syndrome. *Pediatrics* 91: 893–896.

Mitchell, E. A., R. Scragg, A. W. Stewart, D. M. O. Becroft, B. J. Taylor, R. P. K. Ford, I. B. Hassal, D. M. J. Barry, E. M. Allen, and A. P. Roberts. 1991. Results from the first year of the New Zealand cot death study. *NZ Med. J.* 104: 71–76.

Murray, A. B., and B. J. Morrison. 1986. The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma. *J. Allergy Clin. Immunol.* 77(4): 575–581.

Murray, A. B., and B. J. Morrison. 1986. The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma. *J. Allergy Clin. Immunol.* 77(4): 575–581.

Murray, A. B., and B. J. Morrison. 1989. Passive smoking by asthmatics: its greater effect on boys than on girls and on older than on younger children. *Pediatrics* 84(3): 451–459.

Muscat, J. E., and E. L. Wynder. 1995. Exposure to environmental tobacco smoke and the risk of heart attack. *Int. J. Epidemiol.* 24(4): 715–719.

Nicholl, J., and A. O'Cathain. 1992. Antenatal smoking, postnatal passive smoking, and the Sudden Infant Death Syndrome. In *Effects of Smoking on the Fetus, Neonate, and Child*, eds. D. Poswillo and E. Alberman. New York: Oxford University Press, p. 230.

NRC. 1981. *Indoor Pollutants.* Washington, DC: National Academy Press.

NRC. 1986a. *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects.* Washington, DC: National Academy Press.

NRC. 1986b. *The Airliner Cabin Environment: Air Quality and Safety.* Washington, DC: National Academy Press.

O'Connor, G. T., S. T. Weiss, I. B. Tager, and F. E. Speizer. 1987. The effect of passive smoking on pulmonary function and nonspecific bronchial responsiveness in a population-based sample of children and young adults. *Am. Rev. Respir. Dis.* 135: 800–804.

Ostro, B. D. 1989. Estimating the risks of smoking, air pollution, and passive smoke on acute respiratory conditions. *Risk Anal.* 9(2): 189–196.

Ott, W. R. 1999. Mathematical models for predicting indoor air quality from smoking activity. *Environ. Health Perspect.* 107(suppl 2): 375–381.

Palmer, J. R., L. Rosenberg, and S. Shapiro. 1989. "Low yield" cigarettes and the risk of nonfatal myocardial infarction in women. *N. Engl. J. Med.* 320(24): 1569–1573.

Pershagen, G., A. Ericson, and P. Otterblad-Olausson. 1992. Maternal smoking in pregnancy: Does it increase the risk of childhood cancer? *Int. J. Epidemiol.* 21(1): 1–5.

Pirkle, J. L., K. M. Flegal, J. T. Bernert, D. J. Brody, R. A. Etzel, and K. R. Maurer. 1996. Exposure of the US Population to Environmental Tobacco Smoke. The Third National Health and Nutrition Examination Survey, 1988 to 1991. *JAMA* 275(16): 1233–1240.

Ponka, A. 1991. Asthma and low level air pollution in Helsinki. *Arch. Environ. Health* 46: 262–270.

Preston-Martin, S., M. C. Yu, B. Benton, and B. E. Henderson. 1982. N-Nitroso compounds and childhood brain tumors: A case-control study. *Cancer Res.* 42(12): 5240–5245.

Pron, G. E., J. D. Burch, G. R. Howe, and A. B. Miller. 1988. The reliability of passive smoking histories reported in a case-control study of lung cancer. *Am. J. Epidemiol.* 127(2): 267–273.

Pukander, J., J. Luotonen, M. Timonen, and P. Karmer. 1985. Risk factors affecting the occurrence of acute otitis media among 2–3-year-old urban children. *Acta Otolaryngol.* 100: 260–265.

Ra, L. 1992. Passive smoking and hearing loss in infants. *Irish Med. J.* 85: 111–112.

Rebagliato, M., C. d. Florey, and F. Bolumar. 1995. Exposure to environmental tobacco smoke in nonsmoking pregnant women in relation to birth weight. *Am. J. Epidemiol.* 142(5): 531–537.

Remijn, B., P. Fischer, B. Brunekreef, E. Lebret, J. S. Boleij, and D. Noij. 1985. Indoor air pollution and its effect on pulmonary function of adult nonsmoking women: I. Exposure estimates for nitrogen dioxide and passive smoking. *Int. J. Epidemiol.* 14: 215–220.

Repace, J. L., and A. H. Lowrey. 1980. Indoor air pollution, tobacco smoke, and public health. *Science* 208: 464–472.

Repace, J. L., and A. H. Lowrey. 1990. Risk assessment methodologies for passive smoking-induced lung cancer. *Risk Analysis* 10: 27–37.

Repace, J. L., J. Jinot, S. Bayard, K. Emmons, and S. K. Hammond. 1998. Air nicotine and saliva cotinine as indicators of workplace passive smoking exposure and risk. *Risk Analysis* 18(1): 71–83.

Robbins, A. S., D. E. Abbey, and M. D. Lebowitz. 1993. Passive smoking and chronic respiratory disease symptoms in non-smoking adults. *Int. J. Epidemiol.* 22(5): 809–817.

Roquer, J. M., J. Figueras, F. Botet, and R. Jimenez. 1995. Influence on fetal growth of exposure to tobacco smoke during pregnancy. *Acta Paediatr.* 84: 118–121.

Rosen, F. L., and A. Levy. 1950. Bronchial asthma due to allergy to tobacco smoke in an infant: A case report. *JAMA* 144(8): 620–621.

Rosenberg, J., N. L. Benowitz, P. Jacob, and K. M. Wilson. 1980. Disposition kinetics and effects of intravenous nicotine. *Clin. Pharmacol. Ther.* 28: 517–522.

Rubin, B. K. 1990. Exposure of children with cystic fibrosis to environmental tobacco smoke. *N. Engl. J. Med.* 323(12): 782–788.

Rubin, D. H., P. A. Krasilnikoff, J. M. Leventhal, B. Weile, and A. Berget. 1986. Effect of passive smoking on birth-weight. *Lancet* 2(8504):415–417.

Russell, M. A., R. J. West, and M. J. Jarvis. 1985. Intravenous nicotine simulation of passive smoking to estimate dosage to exposed nonsmokers. *Br. J. Addict* 80: 201–206.

Samet, J. M., and P. Lange. 1996. Longitudinal studies of active and passive smoking. *Am. J. Resp. Crit. Care. Med.* 154(6 pt 2): S257–S265.

Samet, J. M., I. B. Tager, and F. E. Speizer. 1983. The relationship between respiratory illness in childhood and chronic airflow obstruction in adulthood. *Am. Rev. Respir. Dis.* 127: 508–523.

Sandler, D. P., A. J. Wilcox, and R. B. Everson. 1985. Cumulative effects of lifetime passive smoking on cancer risk. *Lancet* 1: 312–315.

Sandler, D. P., and D. L. Shore. 1986. Quality of data on parents' smoking and drinking provided by adult offspring. *Am. J. Epidemiol.* 124(5): 768–778.

Sandler, D. P., G. W. Comstock, R. J. Helsing, and D. L. Shore. 1989a. Deaths from all causes in non-smokers who lived with smokers. *Am. J. Public Health* 79: 163–167.

Sandler, D. P., K. J. Helsing, G. W. Comstock, and D. L. Shore. 1989b. Factors associated with past household exposure to tobacco smoke. *Am. J. Epidemiol.* 129(2): 380–387.

Sandler, D. P., R. B. Everson, and A. J. Wilcox. 1985. Passive smoking in adulthood and cancer risk. *Am. J. Epidemiol.* 121: 37–48.

Sandler, D. P., R. B. Everson, A. J. Wilcox, and J. P. Browder. 1985. Cancer risk in adulthood from early life exposure to parents' smoking. *Am. J. Public Health* 74: 487–492.

Sandler, R. S., D. P. Sandler, G. W. Comstock, K. J. Helsing, and D. L. Shore. 1988. Cigarette smoking and the risk of colorectal cancer in women. *J. Natl. Cancer Inst.* 80(16): 1329–1333.

Saracci, R., and E. Riboli. 1989. Passive smoking and lung cancer: current evidence and ongoing studies at the International Agency for Research on Cancer. *Mutat. Res.* 89(2): 117–127.

Savitz, D. A., P. J. Schwingl, and M. A. Keels. 1991. Influence of paternal age, smoking, and alcohol consumption on congenital anomalies. *Teratology* 44(4): 429–440.

Schenker, M. B., J. M. Samet, and F. E. Speizer. 1982. Effect of cigarette tar content and smoking habits on respiratory symptoms in women. *Am. Rev. Respir. Dis.* 125: 684–690.

Schilling, R. S., A. D. Letai, S. L. Hui, G. J. Beck, J. B. Schoenberg, and A. H. Bouhuys. 1977. Lung function, respiratory disease, and smoking in families. *Am. J. Epidemiol.* 106(4): 274–283.

Schoendorf, K. C., and J. L. Kiely. 1992. Relationship of sudden infant death syndrome to maternal smoking during and after pregnancy. *Pediatrics* 90: 905–908.

Schwartz, J., and S. Zeger. 1990. Passive smoking, air pollution, and acute respiratory symptoms in a diary study of student nurses. *Am. Rev. Respir. Dis.* 141: 62–67.

Scientific Committee on Tobacco and Health, and HSMO. 1998. *Report of the Scientific Committee on Tobacco and Health.* The Stationary Office, Report 011322124x.

Seidman, D. S., P. Ever-Hadani, and R. Gale. 1990. Effect of maternal smoking and age on congenital anomalies. *Obstetrics Gynecol.* 76(6): 1046–1050.

Severson, R. K., J. D. Buckley, W. G. Woods, D. Benjamin, and L. L. Robison. 1993. Cigarette smoking and alcohol consumption by parents of children with acute myeloid leukemia. An analysis within morphological subgroups—A report from the Childrens Cancer Group. *Cancer Epidemiol. Biomarkers Prev.* 2: 433-439.

Shephard, R. J., R. Collins, and F. Silverman. 1979. "Passive" exposure of asthmatic subjects to cigarette smoke. *Environ. Res.* 20(2): 392–402.

Slattery, M. L., L. M. Robison, K. L. Schuman, T. K. French, T. M. Abbott, J. C. Overall, and J. W. Gardner. 1989. Cigarette smoking and exposure to passive smoke are risk factors for cervical cancer. *JAMA* 261: 1593–1598.

Sorsa, M., K. Husgafvel-Pursiainen, H. Jarventaus, K. Koskimies, H. Salo, and H. Vainio. 1989. Cytogenetic effects of tobacco smoke exposure among involuntary smokers. *Mutat. Res.* 222(2): 111–116.

Sorsa, M., P. Einisto, K. Husgafvel-Pursiainen, H. Jarventaus, H. Kivisto, Y. Peltonen, T. Tuomi, S. Valkonen, and O. Pelkonen. 1985. Passive and active exposure to cigarette smoke in a smoking experiment. *J. Toxicol. Environ. Health* 16(3–4): 523–524.

Spengler, J. D., and B. G. Ferris Jr. 1985. Harvard air pollution health study in six cities in the U.S.A. *Tokai J. Exp. Clin. Med.* 10(4): 263–286.

Spengler, J. D., D. W. Dockery, W. A. Turner, J. M. Wolfson, and B. G. Ferris Jr. 1981. Long-term measurements of respirable sulfates and particles inside and outside homes. *Atmos. Environ.* 15: 23–30.

Spengler, J. D., R. D. Treitman, T. Tosteson, D. T. Mage, and M. L. Soczek. 1985. Personal exposures to respirable particulates and implications for air pollution epidemiology. *Environ. Sci. Technol.* 19: 700–707.

Stankus, R. P., P. K. Menan, R. J. Rando, H. Glindmeyer, J. E. Salvaggio, and S. B. Lehrer. 1988. Cigarette smoke-sensitive asthma: challenge studies. *J. Allergy Clin. Immunol.* 82: 331–338.

Steenland, K., M. Thun, C. Lally, and C. Heath Jr. 1996. Environmental tobacco smoke and coronary heart disease in the American Cancer Society CPS-II Cohort. *Circulation* 94(4): 622–628.

Stillman, R. J., M. J. Rosenberg, and B. P. Sachs. 1986. Smoking and reproduction. *Fertil Steril* 46(4): 545–566.

Stjernfeldt, M., K. Berglund, J. Lindsten, and J. Ludvigsson. 1986. Maternal smoking during pregnancy and risk of childhood cancer. *Lancet* 1: 1350–1352.

Strachan, D. P., and D. G. Cook. 1997. Health effects of passive smoking: 1. Parental smoking and lower respiratory illness in infancy and early childhood. *Thorax* 52(10): 905–914.

Strachan, D. P., and D. G. Cook. 1998a. Parental smoking and allergic sensitization in children. *Thorax* 53(2): 117–123.

Strachan, D. P., and D. G. Cook. 1998b. Parental smoking, middle ear disease and adenotonsillectomy in children. *Thorax* 53(1): 50–56.

Strachan, D. P., M. J. Jarvis, and C. Feyerabend. 1989. Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children. *Br. Med. J.* 298(6687): 1549–1552.

Svendsen, K. H., L. H. Kuller, M. J. Martin, and J. K. Ockene. 1987. Effects of passive smoking in the multiple risk factor intervention trial. *Am. J. Epidemiol.* 126(5): 783–795.

Tager, I. B. 1988. Passive smoking-brönchial responsiveness and atopy. *Am. Rev. Respir. Dis.* 138: 507–509.

Tager, I. B., A. Muñoz, B. Rosner, S. Weiss, V. Carey, and F. E. Speizer. 1985. Effect of cigarette smoking on the pulmonary function of children and adolescents. *Am. Rev. Respir. Dis.* 131: 752–759.

Tager, I. B., M. R. Segal, A. Muñoz, S. T. Weiss, and F. E. Speizer. 1987. The effect of maternal cigarette smoking on the pulmonary function of children and adolescents: Analyses of data from two populations. *Am. Rev. Respir. Dis.* 136: 1366–1370.

Tager, I. B., S. T. Weiss, A. Muñoz, B. Rosner, and F. E. Speizer. 1983. Longitudinal study of the effects of maternal smoking on pulmonary function in children. *N. Engl. J. Med.* 309: 699–703.

Tainio, V. M., E. Savilahti, L. Salmenpera, P. Arjomaa, M. A. Siimes, and J. Perheentupa. 1988. Risk factors for infantile recurrent otitis media: Atopy but not type of feeding. *Pediatr. Res.* 23(5): 509–512.

Takasaka, T. 1990. Incidence, prevalence, and natural history of otitis media in different geographic areas and populations. *Ann. Otol. Rhinol. Laryngol.* 99: 13–14.

Tashkin, D. P., V. A. Clark, M. Simmons, C. Reems, A. H. Coulson, L. B. Bourque, J. W. Sayre, R. Detels, and S. Rokaw. 1984. The UCLA population studies of chronic obstructive respiratory disease: VII. Relationship between parental smoking and children's lung function. *Am. Rev. Respir. Dis.* 129: 891–897.

Taylor, A. E., D. C. Johnson, and H. Kazemi. 1992. Environmental tobacco smoke and cardiovascular disease: A position paper from the council on cardiopulmonary and critical care, American Heart Association. *Circulation* 86(2): 1–4.

Teele, D. W., J. O. Klein, and B. Rosner. 1989. Epidemiology of otitis media during the first seven years of life in children in greater Boston: A prospective cohort study. *J. Infect. Dis.* 160: 83–94.

Toubas, P. L., J. C. Duke, M. A. McCaffree, C. D. Mattice, D. Bendell, and W. C. Orr. 1986. Effects of maternal smoking and caffeine habits on infantile apnea: A retrospective study. *Pediatrics* 86(1): 159–163.

Trichopoulos, D., A. Kalandidi, and L. Sparros. 1983. Lung cancer and passive smoking: Conclusion of Greek study. *Lancet* 2: 677–678.

Trichopoulos, D., A. Kalandidi, L. Sparros, and B. MacMahon. 1981. Lung cancer and passive smoking. *Int. J. Cancer* 27(1): 1–4.

Trichopoulos, D., F. Mollo, L. Tomatis, E. Agapitos, L. Delsedime, X. Zavitsanos, A. Kalandidi, K. Katsouyanni, E. Riboli, and R. Saracci. 1992. Active and passive smoking and pathological indicators of lung cancer risk in an autopsy study. *JAMA* 268(13): 1697–1701.

Tsimoyianis, G. V., M. S. Jacobson, J. G. Feldman, M. T. Antonio-Santiago, B. C. Clutario, M. Nussbaum, and I. R. Shenker. 1987. Reduction in pulmonary function and increased frequency of cough associated with passive smoking in teenage athletes. *Pediatrics* 80(1): 32–36.

Urch, R. B., F. Silverman, P. Corey, R. J. Shephard, P. Cole, and L. J. Goldsmith. 1988. Does suggestibility modify acute reactions to passive cigarette smoke exposure? *Environ. Res.* 47: 34–47.

van Steensel-Moll, H. A., H. A. Valkenburg, J. P. Vandenbroucke, and G. E. van Zanen. 1985. Are maternal fertility problems related to childhood leukaemia? *Int. J. Epidemiol.* 14(4): 555–559.

Vandenbroucke, J. P., J. H. Verheesen, A. De Bruin, B. J. Mauritz, C. van der Heide-Wessel, and R. M. van der Heide. 1984. Active and passive smoking in married couples: Results of 25 year follow up. *Br. Med. J. (Clin. Res. Ed.)* 84: 1801–1802.

Wald, N. J., K. Nanchakal, S. G. Thompson, and H. S. Cuckle. 1986. Does breathing other people's tobacco smoke cause lung cancer? *Br. Med. J.* 293: 1217–1222.

Wall, M. A., J. Johnson, P. Jacob, and N. L. Benowitz. 1988. Cotinine in the serum, saliva and urine of nonsmokers, passive smokers, and active smokers. *Am. J. Public Health* 78: 699–701.

Wallace, L. A., and E. D. Pellizzari. 1987. Personal air exposures and breath concentrations of benzene and other volatile hydrocarbons for smokers and nonsmokers. *Toxicol Lett.* 35(1): 113–116.

Wang, X., D. Wypij, D. Gold, F. E. Speizer, J. H. Ware, B. G. Ferris Jr., and D. W. Dockery. 1994. A longitudinal study of the effects of parental smoking on pulmonary function in children 6–18 years. *Am. J. Resp. Crit. Care Med.* 149(6): 1420–1425.

Ware, J. H., D. W. Dockery, and A. Spiro, III. 1984. Passive smoking, gas cooking, and respiratory health of children living in six cities. *Am. Rev. Respir. Dis.* 129: 366–374.

Weiss, S. T. 1986. Passive smoking and lung cancer: What is the risk? *Am. Rev. Respir. Dis.* 133: 1–3.

Weiss, B. 1989. Behavior as an endpoint for inhaled toxicants. In *Concepts in Inhalation Toxicology*, eds. R. O. McClellan and R. F. Henderson. New York: Hemisphere Publishing, pp. 475–493.

Weiss, S. T., I. B. Tager, F. E. Speizer, and B. Rosner. 1980. Persistent wheeze: Its relation to respiratory illness, cigarette smoking, and level of pulmonary function in a population sample of children. *Am. Rev. Respir. Dis.* 122: 697–707.

Weitzman, M., S. Gortmaker, and A. Sobul. 1992. Maternal smoking and behavior problems of children. *Pediatrics* 90(3): 342–349.

Weitzman, M., S. Gortmaker, D. K. Walker, and A. Sobol. 1990. Maternal smoking and childhood asthma. *Pediatrics* 85(4): 505–511.

Weitzman, M., S. L. Gortmaker, A. M. Sobol, and J. M. Perrin. 1992. Recent trends in the prevalence and severity of childhood asthma. *JAMA* 268(19): 2673–2677.

Wells, A. J. 1988. An estimate of adult mortality in the United States from passive smoking. *Environ. Int.* 14: 249–265.

White, J. R., and H. F. Froeb. 1980. Small airways dysfunction in nonsmokers chronically exposed to tobacco smoke. *N. Engl. J. Med.* 302: 720–723.

Young, S., P. N. Le Souef, G. C. Geelhoed, S. M. Stick, K. J. Turner, and L. I. Landau. 1991. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N. Engl. J. Med.* 324(17): 1168–1173.

Yue Chen, B. M., L. I. Wan-Xian, and Y. Shunzhang. 1986. Influence of passive smoking on admissions for respiratory illness in early childhood. *Br. Med. J.* 293: 303–306.

Zhang, J., D. A. Savitz, P. J. Schwingl, and W. W. Cai. 1992. A case-control study of paternal smoking and birth defects *Int. J. Epidemiol.* 21(2): 273–278.

Zielhius, G. A., E. W. Heuvelmans-Heinen, G. H. Rach, and P. van den Broek. 1989. Environmental risk factors for otitis media with effusion in preschool children. *Scand. J. Prim. Health Care* 7(1): 33–38.